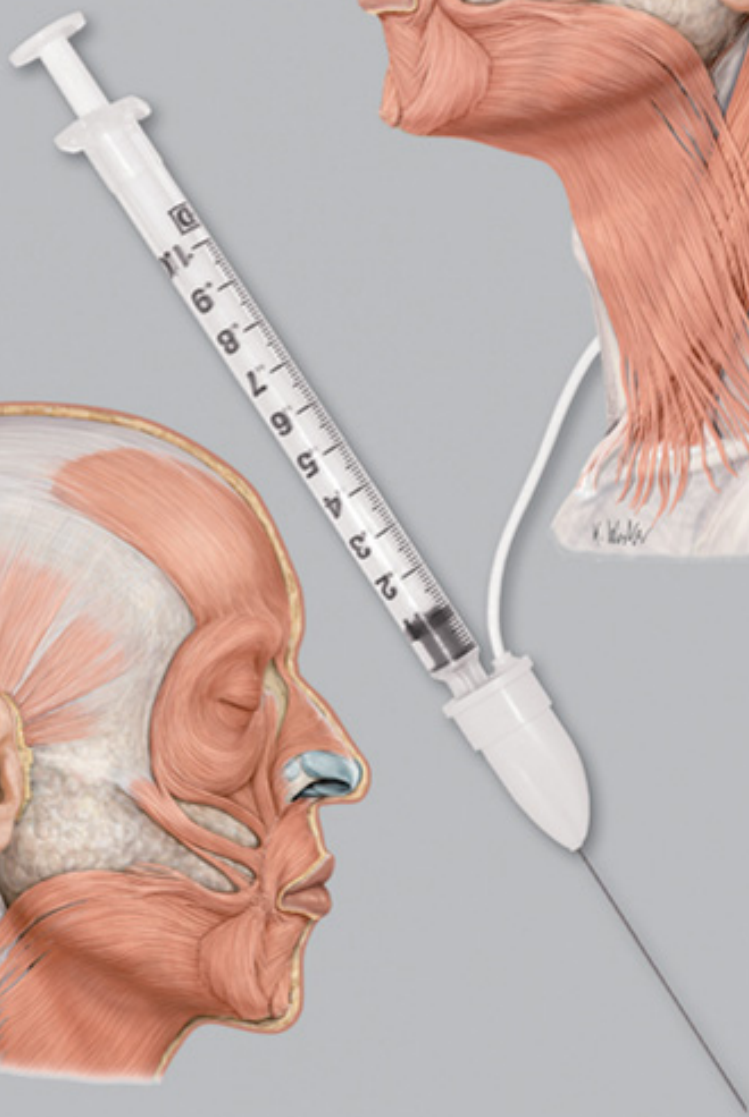
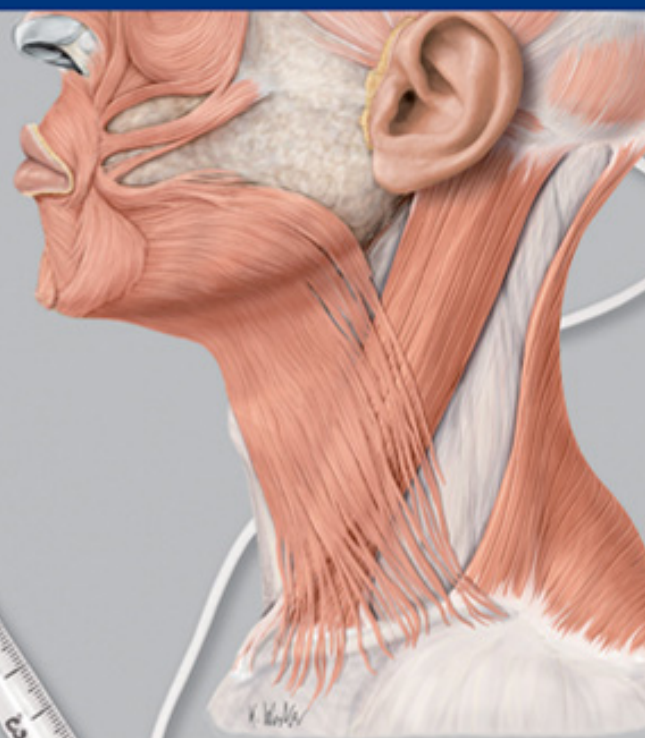


Botulinum Neurotoxin for Head and Neck Disorders

Andrew Blitzer
Brian E. Benson
Joel Guss



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We jointly dedicate this book to our patients, whose persistent efforts to improve the function and quality of their lives constantly challenge, teach, and inspire us.

I additionally dedicate this book to my children, Peter Morgen Blitzer and Polly Blitzer Wolkstein, and my new grandson, Jackson.

—AB

I additionally dedicate this book to my parents; my mentors NP, WV, SOG, APG, SB, and AB; and my wife and children.

—BEB

I additionally dedicate this book to my family for your love and patience, and to my teachers and mentors for sharing your wisdom.

—JG

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Foreword

Botulinum neurotoxin is proving to be one of the most versatile therapies in all of medicine. Well known as a powerful poison, and still responsible for many deaths from botulism around the world each year, botulinum neurotoxin is very safe when used by a physician in carefully controlled circumstances. Ophthalmologist Alan B. Scott first identified the therapeutic potential of botulinum neurotoxin with his studies of strabismus, and since then the therapeutic areas have exploded. Because the toxin blocks neuromuscular junction transmission, the first (and still major) applications were for undesirable muscle spasms. Focal dystonias such as blepharospasm and hemifacial spasm were obvious targets and got early FDA approval. The senior editor of this book, Dr. Andrew Blitzer, is the pioneer who first used botulinum neurotoxin for the treatment of focal dystonia of the laryngeal muscles, spasmodic dysphonia. It turned out that facial wrinkles are due to contraction of small muscles in the skin (who knew that other than dermatologists?), and that these spasms could be

eradicated with botulinum neurotoxin injections. Subsequently, it became clear that botulinum neurotoxin could also block release of other neurotransmitters, and hence could be useful in autonomic disorders such as hyperhidrosis and pain disorders such as migraine headache. The indications are still expanding.

The indications are so broad that most specialists are turning to its use for conditions within their own specialty. Ophthalmologists, otolaryngologists–head and neck surgeons, facial plastic surgeons, neurologists, physiatrists, dermatologists, urologists, gastroenterologists, and rheumatologists now find botulinum neurotoxin therapy valuable. As with any therapy, it must be done right in order to be done successfully. Failures and side effects are often due to poor technique. Therefore practitioners have to learn to do the injections properly. There are various other forums for this such as courses, but it is always nice to have a book such as this handy.

This book emphasizes the use of botulinum neurotoxin injection for those indications in the head and neck. Conditions

range from laryngeal dystonia to facial wrinkles (otolaryngology to dermatology), from palatal tremor to migraine headache (rare to common). It is valuable for any practitioner using botulinum neurotoxin to at least be aware of all the possible uses. Since toxin should not be given more than every three months (at least with current guidelines), patients should not be treated, say, for their blepharospasm on one occasion and their facial wrinkles two weeks later. One physician comfortable with treatment of both conditions might do both in the same sitting.

This how-to-do-it book is supplemented with twenty-two videos of the various techniques. A picture is worth a thousand words and a video is worth a million words. This type of instruction is very valuable. People are good at imi-

tation (now demonstrated to be due, at least in part, to the highly efficient mirror neuron system in the brain). So this text-plus-video can be an important aid to learn and/or to improve technique.

There are no better guides to botulinum neurotoxin therapy around the head and neck than Dr. Blitzer and his co-editors and contributors. Not only was Dr. Blitzer a pioneer, but he has about as much experience as anyone alive. I don't doubt that this book will be valuable to have within ready reach on your bookshelf.

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Preface

This book fills the gap that existed in the medical literature on the management techniques for hyperfunctional, hypersecretory, and pain syndromes of the head and neck. It addresses the motor, sensory, and autonomic nervous systems; reviews the pharmacology of botulinum neurotoxins; and discusses the indications and techniques for their use. Each section is linked to a video of the injection for that indication.

The hyperfunctional motor disorders are discussed in several chapters that address blepharospasm, facial dystonia, Meige's syndrome, oromandibular dystonia, spasmodic dysphonia, and cervical dystonia. The chapters review the diagnosis and phenomenology of these disorders, and discuss the approaches to using toxin therapy in the different muscles. Other hyperfunctional disorders reviewed here include hemifacial spasm and facial synkinesis, facial lines and wrinkles, upper and lower esophageal spasm, and palatal myoclonus. Several chapters discuss the effects of toxin on the afferent nervous system and pain syndromes. The effects of the release of

peripheral pain mediators and the consequent change in central pain thresholds are reviewed. Specific treatment approaches to pain are addressed in chapters on migraine and chronic daily tension headaches, temporomandibular disorders, and trigeminal neuralgia. Management of autonomic nervous system disorders is also reviewed, and specific management of autonomic disorders such as Frey's syndrome, facial hyperhidrosis, and sialorrhea is discussed.

This book should be of value for clinicians who provide care to patients with hyperfunctional motor disorders, pain and sensory disorders, and secretory disorders of the head and neck. These clinicians include otolaryngologists—head and neck surgeons, neurologists, dentists, pain specialists, physical medicine and rehabilitation specialists, and all others who treat these disorders. The book can serve as a guide to using botulinum neurotoxin therapeutically to treat patients with motor, sensory, and autonomic nervous system disorders of the head and neck.

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Pharmacology of Botulinum Neurotoxins

Andrew Blitzer and Conor J. Gallagher

Botulinum neurotoxin (BoNT) has been approved as a safe and effective therapeutic option for several clinical conditions. The common basis underlying all of the conditions amenable to treatment with BoNT is overactivity of neurotransmitter or neuropeptide release. The clinical efficacy of BoNT is based on the localized and highly specific, but reversible, disruption of the exocytotic mechanism within neurons, resulting in temporary inhibition of the release of neurotransmitters after injection into specific muscles or other tissues.

Botulinum neurotoxins are synthesized by a variety of clostridial species, most notably *Clostridium botulinum*, but also including *C. baratii* and *C. butyricum*.¹ These bacteria synthesize several immunologically distinct neurotoxins classified as serotypes A through G. The biologic activity of the neurotoxin is contained within a 150-kd protein com-

monly referred to as the core neurotoxin. In nature, a single 150-kd neurotoxin is incorporated into a molecular complex that varies in size based on the number of associated nontoxic proteins, which are classified as hemagglutinins or nonhemagglutinins.² The largest neurotoxin complex is 900 kd, formed only by the A serotype. Serotypes A, B, C1, and hemagglutinin-positive D are in the form of 500-kd and 300-kd complexes, whereas serotypes E, F, and hemagglutinin-negative D form only 300-kd complexes.³ The neurotoxin complex is known to stabilize and protect the core neurotoxin against thermal and pH stress in addition to shielding the neurotoxin from enzymatic degradation.⁴⁻⁶

The core neurotoxin is synthesized as a 150-kd single-chain protein that must be cleaved or “nicked” by proteases to exert its activity.⁷ Cleavage produces a di-chain molecule consisting of a 100-kd

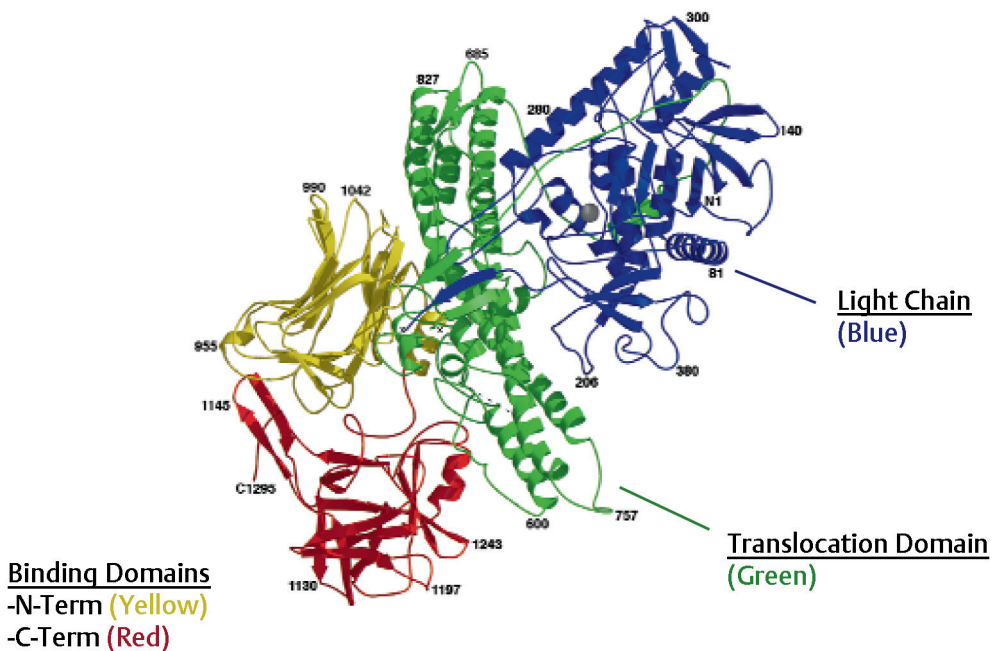


Fig. 1.1 Botulinum neurotoxin (BoNT) molecular structure. (From Lacy DB, Tepp W, Cohen AC, et al. Crystal structure of botulinum neurotoxin type A and implication for toxicity. *Nat Struct Biol* 1998;5:898–902. Reprinted by permission.)

heavy chain and a 50-kd light chain that are held together by a disulfide bond.

The activated di-chain molecule consists of three functional domains, each playing a defined role in the mechanism of action of the neurotoxin: the C-terminal portion of the heavy chain contains the binding domain, responsible for docking the neurotoxin to the neuronal surface; the N-terminal portion of the heavy chain contains the translocation domain, whereas the light chain contains the catalytic domain responsible for cleavage of the intracellular target of BoNT (**Fig. 1.1**). The tertiary structure of the di-chain protein is conserved through all clostridial neurotoxins; however, there is considerable heterogeneity between the protein sequences of the different

serotypes (reportedly up to 70%), accounting for their different neuronal affinities, antigenicity, and intracellular targets.⁸

In the treatment of skeletal muscle overactivity BoNTs inhibit acetylcholine release at the neuromuscular junction, thereby reducing excessive muscle contractions. This inhibition of calcium-dependant vesicular neurotransmitter release occurs via a multiple-step process.

In the first step, the neurotoxin must dissociate from its protective protein shield to allow binding of the free neurotoxin to the neuronal surface. The kinetics of dissociation *in vivo* are currently unknown, but the stability of the neurotoxin complex is known to be af-

fectured by basic pH and increasing ionic strength of the solute.^{9,10}

The binding of the free BoNT to the neuron is accomplished through the interaction of the heavy chain of the 150-kd neurotoxin with neuronal receptors that are located predominantly, but not exclusively, on cholinergic nerve terminals. For BoNT/A (the most commonly used in clinical practice), a two-receptor mechanism has been proposed: the neurotoxin first interacts with a cell-surface resident ganglioside that serves to retain the neurotoxin close to the plasma membrane, facilitating the binding of the neurotoxin with its cognate protein receptor. The protein receptor for type A, E, and F neurotoxins has been identified as SV2, a constituent protein of the synaptic vesicle.^{11–14} The neurotoxin is only able to bind to SV2 when the protein is exposed on the cell surface during neurotransmitter release. Thus, the neurotoxin preferentially enters neurons that are actively secreting neurotransmitter or neuropeptides.¹¹ The receptor molecules for serotypes A and B are distinct, with the protein receptor for types B and G identified as another synaptic vesicle protein known as synaptotagmin.¹³ Other serotypes may also bind to unique sites, but they have not been characterized at this time.

After binding, BoNTs are internalized into the neuron via receptor-mediated endocytosis.¹⁵ The neurotoxin undergoes a conformational change inside the acidified endocytotic vesicles, allowing the translocation domain to interact with the membrane of the endocytotic vesicle, providing a portal to enable the light

chain to traverse the wall of the endosome.¹⁶ The low pH in the endocytotic vesicle also reduces the disulfide bond, which releases the light chain from the heavy chain, freeing it to enter the neuronal cytosol.¹⁷ Once inside the cytosol, the light chain, which contains a zinc-dependent endopeptidase, disrupts one or more of the SNARE (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor) proteins necessary for vesicle docking and fusion, thereby reducing exocytotic neurotransmitter release¹⁸ (**Fig. 1.2**). Each serotype cleaves a specific peptide bond on one or more of these proteins. Type A neurotoxin cleaves the membrane-associated SNARE protein SNAP-25, whereas type B neurotoxin cleaves the vesicular-associated protein VAMP (synaptobrevin). It has been recently proposed that modulation of the interstitial zinc concentration might alter the clinical efficacy of BoNT activity; however, this concept remains unexplored at this time.

The relative duration of inhibition of neurotransmitter release varies among serotypes, presumably based on the half-life of the light-chain¹⁹ and the time it has taken for the neuron to restore intact SNARE proteins (**Fig. 1.3**). In a preclinical model, the duration of effect was the longest for type A, followed by types C1, B, F, and E.²⁰ Following injection in human muscles, serotypes A and C1 appear to have the longest duration of effect.²¹

The recovery of neuronal activity following BoNT-induced denervation has been examined in several preclinical models.^{22–24} Early studies showed that axonal sprouts developed from the af-

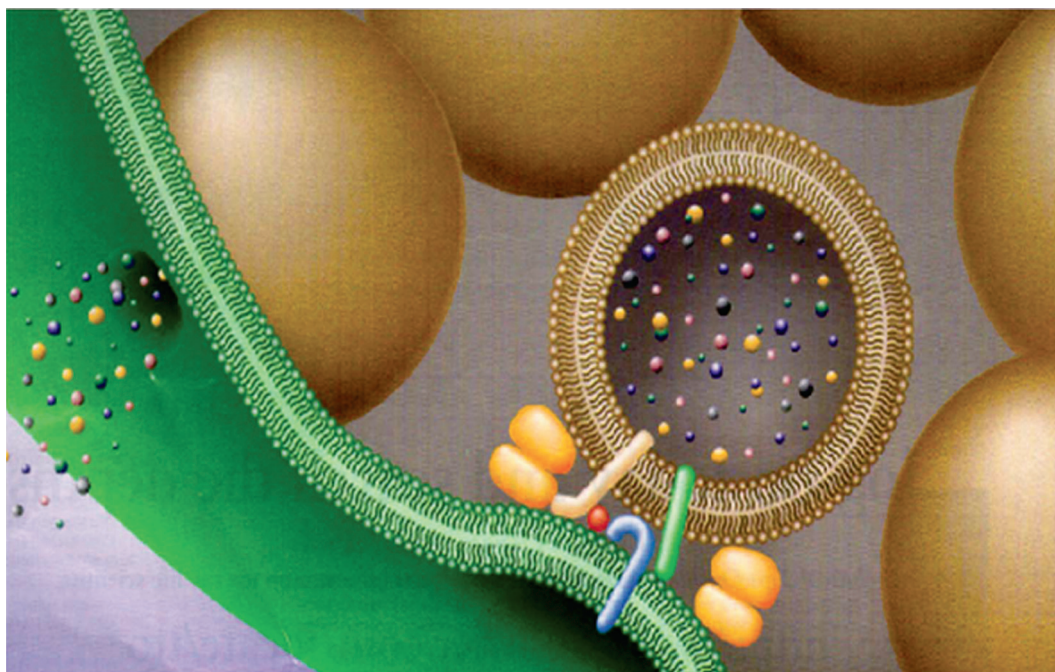


Fig. 1.2 Inhibition of exocytosis. (From Martin TF, Stages of regulated exocytosis. *Trends Cell Biol.* 1997 Jul;7(7):271–6.)

affected nerves, likely in response to growth factor secretion from the denervated muscle. These sprouts are active and produce temporary reinnervation during the early recovery phase. The exact duration of the pharmacologic action of BoNT in neurons is not known; however, during the later phase of recovery, vesicular release has been found to return at the original terminal, a process that is accompanied by retraction of the neuronal sprouts. This suggests a process of sprouting that is associated with reestablishment of activity over time in the originally affected nerve terminal.

The inhibition of neurotransmitter release by BoNTs is reversible, which has both benefits and limitations in clinical use. The benefits include the flexibility

to inject a given muscle based on its activity level, which may fluctuate over time, the avoidance of permanent interventions such as surgery, and the resolution of any unintended effects of BoNT treatment. The primary limitation associated with the reversibility of the effects of BoNT is the need for repeated injections; however, repeat treatment can result in sustained efficacy. As most conditions treated with BoNT are chronic in nature, a longer duration of effect is a desirable property and was the rationale for the development of type A over other serotypes of BoNT for clinical use.

In addition to the inhibition of acetylcholine release from alpha motor neurons, BoNT/A also inhibits neurotransmitter release from gamma motor

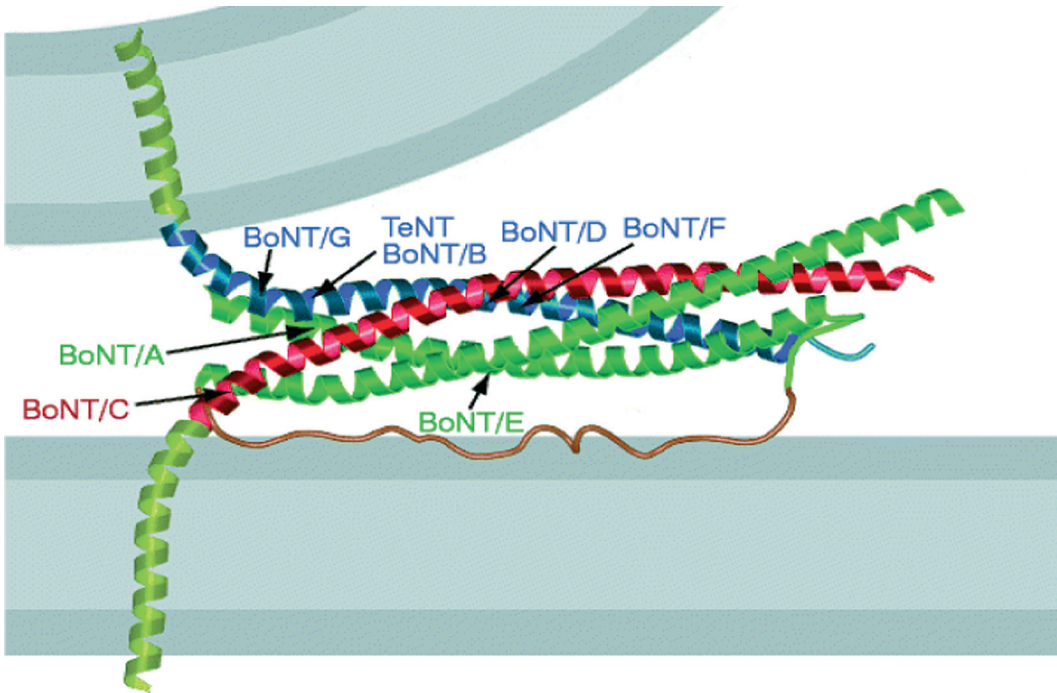


Fig. 1.3 BoNT cleavage sites. TeNT = tetanus neurotoxin. (From Sutton RB, Fasshauer D, Jahn R, Brunger AT. Crystal structure of a SNARE complex involved in synaptic exocytosis at 2.4 Å resolution. *Nature* 1998;395:347–353. Reprinted by permission.)

neurons innervating the intrafusal fibers of the muscle spindle.^{25–27} The gamma motor system contributes to the setting of muscle tone and is known to play an important role in the maintenance of hyperactive muscle contractions in spasticity and dystonia. Reducing the gamma efferent influence in these conditions reduces the afferent feedback through 1a afferent neurons, perhaps modifying, at a spinal level, the altered sensorimotor integration that occurs in these conditions.²⁸ At least some muscles of facial expression are reported to lack muscle spindles^{29,30}; therefore, the contribution of this effect in the aesthetic applications of BoNT in the face is unclear.

Botulinum neurotoxin has been reported to be effective in managing hyperfunction of sweat glands (hyperhidrosis)³¹ and salivary glands (sialorrhea),³² in addition to other secretory conditions such as rhinitis³³ and gustatory sweating.³⁴ This suggests that injections of BoNT into appropriate tissues also has an effect on the activity of postganglionic neurons of the autonomic nervous system.³⁵ By blocking acetylcholine release in these fibers, glandular secretions may be reduced or blocked. In relative terms, BoNT/A appears to have a significantly longer duration of effect on autonomic neurons, with clinical benefit persisting as long as 6 to 9 months in disorders such as hyperhidrosis and

overactive bladder in contrast to the 3 to 4 months typically observed for striated muscle.^{31,36} This may reflect a difference in the recovery mechanisms in autonomically innervated versus somatically innervated tissue; for example, there is evidence that axonal sprouting does not occur to the same degree in the bladder following BoNT as it does in striated muscle³⁷; however, other factors may also be involved.

Beyond the effects of BoNT on muscle tone and glandular secretions, BoNT/A has also been reported to reduce pain associated with cervical dystonia,³⁸ temporomandibular disorders,³⁹ and post-herpetic⁴⁰ and trigeminal neuralgia.⁴¹ Furthermore, recent data have demonstrated that one BoNT product, onabotulinumtoxinA is effective in decreasing the frequency of headaches in patients with chronic migraine.⁴² The mechanism of action of the neurotoxin in these conditions is unclear; however, it has been proposed that it occurs through the inhibition of release of neuropeptides and neurotransmitters from the peripheral terminals of afferent neurons.^{43,44}

C-fiber nociceptive neurons are known to release glutamate and proinflammatory neuropeptides such as substance P and calcitonin gene-related peptide (CGRP) from their peripheral terminals in response to activation.⁴⁵ Release of substance P and CGRP results in vasodilation⁴⁶ and extravasation of other inflammatory mediators such as bradykinin, prostaglandins, histamine, and serotonin.⁴⁷ These inflammatory mediators either directly stimulate or sen-

sitize peripheral nociceptors, triggering the sensation of pain and peripheral sensitization.⁴⁷ The sensitization of peripheral nociceptors may, in turn, trigger the release of more substance P and glutamate in the spinal cord, potentially leading to central sensitization, driving chronicity of pain.⁴⁸ Peripherally released glutamate is also believed to stimulate nociceptive neurons through activation of receptors on peripheral afferents.⁴⁹ SNARE proteins have been shown to mediate the release of these neuropeptides and neurotransmitters,⁵⁰ and thus the mechanism underlying the antinociceptive action of BoNT type A is thought to involve inhibition of release of these factors leading to a direct reduction of peripheral sensitization and, subsequently, an indirect reduction in central sensitization.

Newer data suggests a potential addition to the antinociceptive effects of BoNT. TRPV1 is an ion channel found on some sensory neurons that is activated by capsaicin, protons, and noxious heat, and is known to be upregulated in tissues during chronic pain and inflammation.⁵¹ Botulinum neurotoxin type A has been shown to reduce the expression of TRPV1 in several cell and tissues types, suggesting another mechanism by which BoNT can potentially reduce peripheral sensitization.^{52–54}

A-delta sensory fibers, which mediate acute pain signals, or A-beta fibers, which mediate touch and pressure sensation, do not release neuropeptides or transmitters from their peripheral terminals and are therefore not affected by BoNT.

Thus, BoNT does not induce cutaneous anesthesia or interfere with the normal perception of acute pain.

■ Conclusion and Future Directions

The number of approved indications for BoNT has grown significantly since this agent was first proposed as a therapeutic tool in the 1970s, and many other potential uses have been reported in the literature. This can be attributed to the exquisite specificity of BoNTs on vesicular neurotransmitter release. With a greater understanding of the pharmacology, it is conceivable that the range of clinical indications for BoNT will grow in the future.

Combining advances in the pharmacology with advances in molecular biology and protein synthesis technology has facilitated the creation of recombinant proteins, synthesized in *Escherichia coli*. These techniques have enabled investigators to modify the protein structure of the neurotoxin to create “designer” toxins with altered neuronal specificity, and may, in the future, lead to development of neurotoxins targeted to very specific neuronal subtypes, or with altered pharmacologic properties.^{55–57}

The development of alternative delivery systems for BoNTs has also been proposed, and clinical trials evaluating the efficacy of a topically applied neurotoxin formulation in crow’s feet lines and hyperhidrosis are in development.^{58,59}

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■ S E C T I O N I ■

Dystonia

Blepharospasm

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Blepharospasm is a dystonia of the facial musculature that ranges in severity from an increased blink rate to disabling contractions with pain and visual dysfunction. As with all dystonias, the disorder involves involuntary sustained muscle contractions. Not long ago, dystonias were thought to be manifestations of psychiatric disease. Today, they are understood to be complex neurologic disorders with abnormalities in sensory input, central processing, and motor output, interacting to produce the movement disorder.¹ The primary muscle involved is the orbicularis oculi. Other protractors of the eyelids include the corrugator superciliaris and procerus muscles. Spasms are usually bilateral but may affect one side primarily. Blepharospasm most commonly presents as a focal dystonia often referred to as benign essential blepharospasm. Meige’s syndrome or segmental cranial dystonia

is the association of blepharospasm with oromandibular and sometimes cervical or laryngeal dystonia.²

Blepharospasm is uncommon, with an estimated prevalence of up to one case per 10,000 people. There is an increased female to male prevalence. Mean age of diagnosis is in the sixth decade of life.³ The condition usually begins with increased blink rate or spasms of the eyelids, forehead, or midfacial muscles. Patients often complain of eye irritation, pain, photophobia, or abnormal tearing, and may initially be diagnosed with various other ocular disorders. Spasms may be triggered by sensory stimulation such as wind, air pollutants, or bright light, and may be worse in stressful situations. Some patients identify sensory tricks such as touching the face, using artificial tears, or talking and singing that may temporarily abate the spasm. The condition is often progressive and

results in functional blindness in a significant minority of those affected.⁴ Patients may avoid social settings, reading, driving, or watching television, with ensuing anxiety and depression. Maximum disability is reached at an average of 3 years after onset. Although severity may fluctuate, spontaneous remissions are rare. Over the long term, the persistent contractions can result in weakening of the eyelid's fascial attachments, resulting in brow ptosis, dermatochalasis, and ectropion, with further visual field obstruction. The disease typically remains focal but may involve other facial muscles or, rarely, other parts of the body.

Management begins with treatment of any underlying eye disorder such as blepharitis, conjunctivitis, or corneal irritation, and with lid hygiene and lubrication. Tinted sunglasses with ultraviolet blocking have demonstrated efficacy as well.⁵ Some patients resort to “eyelid crutches” or springs on glasses to hold lid open. Systemic medications such as benzodiazepines and the antiparkinsonian agent Artane have limited efficacy and significant adverse effects.² Surgery is reserved for patients who fail more conservative treatments. Neurectomy of facial nerve branches has generally been abandoned in favor of myectomy of the eyelid protractors.

Botulinum neurotoxin (BoNT) injection has emerged as a treatment of choice for blepharospasm, and it is approved by the United States Food and Drug Administration (FDA) for this application. Many studies ranging from large open label to small double-blind placebo-controlled

have demonstrated BoNT injection to be both effective and safe, with success rates exceeding 90%.^{6–10} The American Academy of Neurology Therapeutics and Technology Assessment Subcommittee rates the strength of evidence behind the use of BoNT for blepharospasm as level B, meaning it is “probably effective.”¹¹ A higher level recommendation requires at least two large double-blind placebo-controlled studies with rigorous requirements. Unfortunately, no such studies have been performed.¹² Long-term efficacy and safety have been demonstrated as well.^{9,13,14}

■ Workup

Diagnosis of blepharospasm is clinical, though it may initially be challenging as there is overlap between early symptoms of blepharospasm and other eye disorders. A history of other neurologic symptoms, use of psychotropic medications, and family history of dystonia should be elicited. All patients benefit from an ophthalmologic examination. Further studies and imaging should be obtained to rule out a central nervous pathology when appropriate.

Apraxia of eyelid opening is an important diagnosis that may be difficult to differentiate from blepharospasm. Like blepharospasm, it also presents with abnormal eyelid closure but is primarily due to involuntary inhibition of the levator palpebrae muscle. Examination of the lower eyelid usually shows elevation in patients with blepharospasm. This diagnosis is an important consideration

when BoNT treatment fails to improve blepharospasm.¹

■ Anatomy

The orbicularis oculi muscle lies in a plane just deep to the subcutaneous tissue and is divided into orbital and palpebral parts. The orbital portion forms a wide circle around the orbital rims and interdigitates with other facial muscles. It is under voluntary control and is responsible for tight closure of the eyelids. The palpebral orbicularis muscle involuntarily and gently closes the eye during blinking and sleep and is further divided into a preseptal portion that overlies the orbital septum and a pretarsal portion that extends between the medial and lateral canthi anterior to the tarsus (**Fig. 2.1**). The skin of the eyelids is the thinnest skin in the body and contains very little subcutaneous fat. Thus,

the orbicularis oculi muscle may lie just 1 mm below the surface of the skin. In the brow and cheek regions, the skin becomes considerably thicker.

■ Technique

Injections are performed with 1-mL syringes and 30- or 32-gauge short needles. Electromyography (EMG) is not necessary to guide injection due to the consistent subcutaneous location of these muscles. The dose and exact location of each injection is tailored based on the results of previous injections. To start, Botox is diluted to a concentration of 2.5 to 5 units (U) per 0.1 mL. The orbicularis oculi is initially treated with a somewhat low starting dose of 12 to 15 U per side, although higher doses may be required. The orbital portion of the orbicularis muscle is injected at three to six sites peripherally to the orbital rim with

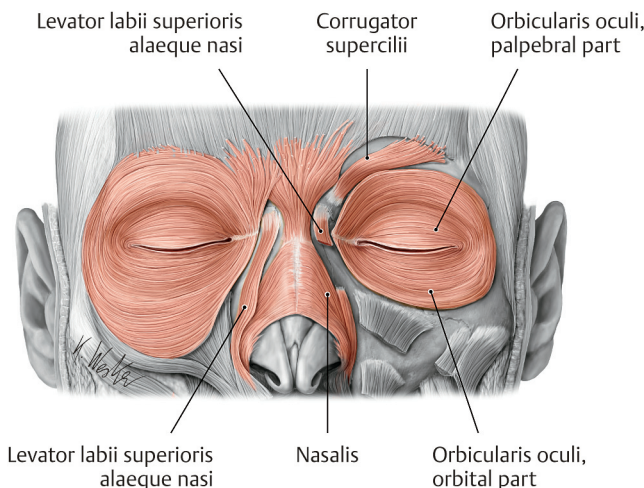


Fig. 2.1 Anatomy of the orbicularis oculi muscle. (From THIEME Atlas of Anatomy, Head and Neuroanatomy, © Thieme, 2007, Illustration by Karl Wesker.)



Fig. 2.2 Injection of the lateral orbital portion of the orbicularis oculi.

2.5 to 5 U of Botox in an injection volume of 0.1 mL. It is recommended to avoid injection directly over the meridian of the eye to minimize diffusion to levator palpebrae with subsequent ptosis as well as to avoid the inferomedial orbicularis muscle to prevent diffusion to the inferior oblique muscle and to avoid interference with the lacrimal drainage apparatus (**Figs. 2.2 and 2.3**). The superior palpebral portion of the muscle is injected with 1.25 U of Botox in a volume of 0.05 mL at two sites medially and laterally, again avoiding the middle of the eyelid (**Figs. 2.4 and 2.5**).

■ Follow-Up

Mean onset of action takes place around 3 to 5 days after injection, with peak ef-

fect at around 1 to 2 weeks. The average duration of effect is approximately 3 months, although some patients experience longer lasting relief of up to 6 months. Patients should maintain a diary of symptoms and side effects to help guide future injections. Treating physicians should carefully document each injection site and dose. Inadequate reduction of spasm should prompt an increase in dose. Consider injecting the pretarsal portion of the orbicularis oculi muscle with a low dose (e.g., 1.25 U of Botox), although this may produce unwanted effects. If associated muscles such as the corrugator superciliaris and procerus muscles are involved, they may benefit from injection as well. Adverse effects (see below) indicate the need for lower doses or avoiding certain injection sites.



Fig. 2.3 Injection of the upper orbital portion of the orbicularis oculi.



Fig. 2.4 Injection of medial palpebral portion of the orbicularis oculi.

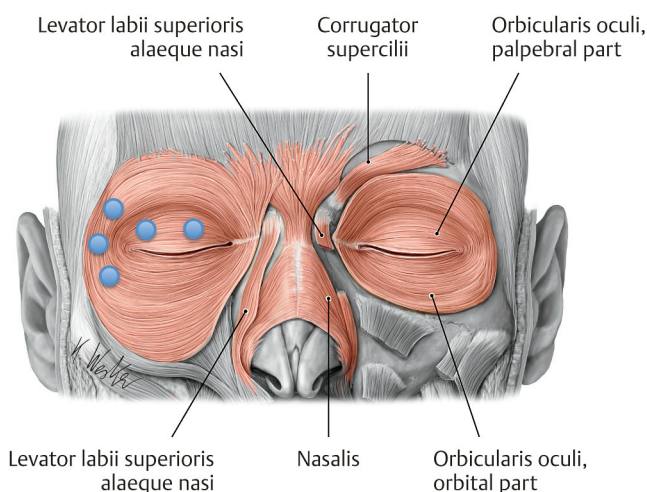


Fig. 2.5 Anatomy of orbicularis muscle with injection points. (From THIEME Atlas of Anatomy, Head and Neuroanatomy, © Thieme, 2007, Illustration by Karl Wesker.)

■ Complications and Pitfalls

Discomfort and bruising may be decreased by using smaller injection volumes and minimizing the number of injection sites. Side effects related to BoNT are more common during the early dose-optimizing period. Dry eyes and partial ptosis due to weakening of the levator palpebrae muscle are the most common side effects. Lagophthalmos may occur, and patients should be instructed to protect their eyes to prevent corneal exposure. Diplopia is rare, occurring in less than 1% of cases.¹⁵ All of these adverse effects are generally

self-limited. Proper education and informed consent are important so that patients know what to expect.

■ Conclusion

Blepharospasm is a debilitating neurologic disorder that can result in functional blindness. BoNT injection has emerged as a first-line treatment of choice. Knowledge of periorbital anatomy, careful attention to technique, and proper patient education are critical to obtaining good results.



Video 1 Blepharospasm

An analysis of the areas of hyperfunctional muscle contraction of the orbicularis oculi is done. In general, six places are injected, including two in the upper eyelid. These are placed very lateral and medial, so as not to allow for migration of the toxin to the central area and the levator muscle. Weakening this muscle will produce ptosis. Additional points are injected laterally along the orbital rim. If there is a supraorbital component, additional toxin may be given medially or laterally above the brow.

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3

Facial Dystonia

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Dystonias of the facial region can be classified in a variety of ways. Dystonic movement disorders can affect the upper face, mid-face, lower face, and/or cervical region. Individual dystonias present at a variety of age ranges and with a range of frequency. This chapter briefly describes several facial dystonias and similar craniofacial muscle disorders. Many are covered in further depth in later chapters.

Benign essential blepharospasm is a focal dystonia that results in an involuntary closure of the musculature around the eye. This involuntary movement is typically chronic and persistent in nature, resulting in a functional blindness in which there is an intact visual pathway. Although rare (1 in 20,000), it tends to occur in the fifth and sixth decades of life. Botulinum neurotoxin (BoNT) injection to the local musculature has proven effective in many reported trials.¹⁻³

Hemifacial spasm, first described by Gowers in 1884, is not a dystonia but a segmental myoclonus resulting in a re-

current, involuntary, synkinetic dystonic muscular contractions of the face. The muscles in contracture are those innervated by the facial nerve and are typically unilateral. There are rare cases of bilateral involvement. It typically occurs in the fourth and fifth decade of life with a prevalence of 1 in 10,000 and typically first presents in the orbicularis oculi. The most common cause of facial nerve interruption is believed to be an aberrant vascular loop (from the posterior inferior cerebellar artery) causing local compression.⁴ Other causes of compression may include local tumor, vascular malformation, and infectious processes. Hemifacial spasm can be misdiagnosed as isolated blepharospasm, orbicularis oculi myokymia, or synkinetic movements post-Bell's palsy. Therefore, it is important to thoroughly evaluate and correctly diagnose all dystonias. Anticonvulsive medication, such as oral doses of carbamazepine or valproic acid, helps to control central myoclonus. Intramuscular injec-

tion of BoNT reliably reduces synchronous spasms in a safe, repeatable way.⁵⁻⁷ Defazio et al⁸ reported a 95% response rate and with others, corroborated the effectiveness of BoNT/A in relieving the symptoms of primary hemifacial spasm.⁹

Oromandibular dystonia (OMD) is characterized by dystonic muscular contractions affecting the jaw, mouth, and lower face. In more severe cases, the tongue musculature may be involved. In patients with OMD, involuntary contractions may involve the muscles that open the jaw and close the jaw, and muscles of mastication. This leads to a significant variety of presentations in OMD. Associated findings may include spasms of jaw closure with difficulty opening the mouth, jaw clenching or bruxism, spasms of jaw opening, and sideways deviation or protrusion of the jaw. Additional symptoms may also be present, such as lip tightening/pursing, retraction of the corners of the mouth, and deviation or protrusion of the tongue. Because these findings vary in presentation but are localized, many patients with OMD may present with jaw pain, eating difficulties, or dysarthria.

Dystonic spasms can sometimes be provoked by certain activities, such as talking, chewing, or biting. There have been reported incidences of medications causing orofacial dystonia or tardive dystonia, such as weak serotonin reuptake inhibitor, but no exact mechanism has been found.¹⁰ Particular sensory tricks may help to temporarily alleviate a patient's OMD symptoms. Reports of successful sensory tricks include chewing gum, talking, placing a toothpick in

the mouth, lightly touching the lips or chin, or applying steady pressure in the submental region. Dystonic spasms may extend to involve nearby areas including the muscles of the eyelids, nose, neck, or vocal cords. Although some medications have been used, their efficacy is low in OMD. BoNT is the preferred treatment for all types of OMD but is most effective in the jaw-closure subtype.^{2,9,11,12} Tongue injections are contraindicated due to the risk of aspiration.

Meige's syndrome is the combination of blepharospasm and oromandibular dystonia. As with OMD, the presentation varies. It is possible for a patient to progress from a simple blepharospasm to Meige's syndrome as the disease process progresses. All patients diagnosed with Meige's syndrome have the presence of some component of blepharospasm and OMD. BoNT is the treatment of choice, and the treatment is tailored to the patient's symptomatology.^{9,11,12}

Cervical dystonia, also known as spasmodic torticollis, is a focal dystonia that affects the neck and shoulders. These dystonic movements cause postural abnormalities and discomfort and can be tonic, clonic, or tonic-clonic in nature. Similar to OMD, sensory tricks can be used to relieve some of the symptoms temporarily. Treatments include anticholinergic medications, and BoNT injections to the affected musculature.¹¹

Focal dystonias exist beyond blepharospasm, OMD, and cervical dystonia. Although the majority of dystonias affecting the lower face also affect the jaw (OMD), one can have local focal dystonia of just the lower face or a localized re-

gion of the lower face. These focal dystonias are typically treated with local injection of BoNT to the affected area every 3 to 4 months as needed. If the disease continues to progress, the dystonia may spread beyond its initial site, leading to a diagnosis of OMD, Meige's syndrome, or even more generalized dystonias.

Other facial manifestations of muscle contractions exist and may mimic the symptoms of a focal dystonia. Craniofacial tremor, which occurs in association with essential tremor, Parkinson's disease, and electrolyte imbalances, are in fact focal motor seizures. The facial manifestations are typically postictal with noted weakness of the face—most often the lower face.

Facial chorea, a non-patterned movement disorder, occurs in the context of a more systemic movement disorder.

Facial tics, on the other hand, are repetitive, partially purposeful, succinct movements of the face. Medications, physiologic changes, and encephalopathy are typical causes of tic disorders.

Facial myokymia also presents with repetitive, succinct movements but usually begins at the vermillion border and spreads in a wave-like pattern. Myokymia is typically idiopathic and resolves over weeks to months without any further treatment.

■ Workup

Dystonias and dystonic-like muscular contractions of the facial region are varied in nature and location. Therefore,

discerning the individual dystonia depends on the presentation. A comprehensive history and physical examination should be able to distinguish essential blepharospasm, OMD, cervical dystonia, Meige's syndrome, and more localized dystonias. Other facial manifestations of musculature contractions such as craniofacial tremor, facial tics, facial chorea, facial myokymia, and hemifacial spasm may be misdiagnosed as dystonias. However, their subtle presentations (facial myokymia's wave-like spread pattern; craniofacial tremor's postictal presentation; facial tic's repetitive, succinct movements) should facilitate distinguishing them.

■ Anatomy

The facial muscular anatomy is complex, with 30 individual muscles. It is important to recognize the facial musculature that is affected and how it can cause facial asymmetry. Whether the dystonia or dystonic-like syndrome is unilateral (hemifacial spasm), localized to the lower face (craniofacial tremor, localized OMD), or affecting multiple sites (Meige's syndrome), identifying the individual muscles affected facilitates treatment planning. When creating a treatment plan for the dystonia, postinjection symmetry is also an important consideration.

■ Techniques and Treatments

Treatments of facial dystonias can entail oral medication, intramuscular injection

of BoNT, or surgical intervention. BoNT is the typical treatment of choice, but it only affects the local area of injection. Electromyography monitoring enables better localization of the muscles affected. Injections typically last 3 to 4 months and need to be repeated as the effect of the BoNT fades. BoNT injections have the advantage of being simple, safe, and usually indefinitely repeatable in most cases. Several open and a few controlled studies report good to excellent improvement of OMD or blepharospasm in 76 to 100% of the patients injected.

Oral medication can be used as single treatment modality or in combination with BoNT for better neurologic control of dystonia. Surgical intervention is rare and is reserved for those who fail both oral medication and BoNT injections.

■ Complications

Complications can occur from local diffusion or excessive response of toxin into unintended musculature. If a blepharospasm patient's injection diffuses into the levator muscle, the patient might experience weakness of the levator muscle and have subsequent ptosis. If this occurs, it is possible to help stimulate the muscle with a sympathomimetic drug such as apraclonidine, 0.5 to 1.0% drops. OMD patient's injections into the pterygoids, masseters, or temporalis

musculature can cause excessive jaw opening. Injections near the tongue/tongue base can cause significant dysphagia. Local lower face injections into the zygomaticus and risorius may flatten the nasolabial line and may change the smile and cause an asymmetric drooping of the angle of the mouth. These are dose-related events that may be corrected with smaller doses on future visits.

■ Conclusion

There are many different classifications of facial dystonia, including blepharospasm, OMD, and cervical dystonia. Meige's syndrome is a combination of blepharospasm and OMD. Localized dystonias also can occur separate from the more common syndromes and occasionally progress. Hemifacial spasm is in fact not a dystonia but a segmental myoclonus. Hemifacial spasm, craniofacial tremor, facial chorea, facial tics, and facial myokymia all can be misdiagnosed as a dystonia. It is crucial to obtain an excellent history and physical examination to distinguish these confusing entities. BoNT is a mainstay of treatment for all facial dystonias. Oral medication is frequently used in conjunction with botulinum injections, but can also be used as a single treatment modality in rare cases.



Video 2 Lower Facial Dystonia

Injecting the mentalis muscle and the depressor angli oris will help prevent the “peau d’orange” chin and the pulling down of the corners of mouth and lower lip. Patients with lower facial dystonia may also need injections to the upper platysma muscle to prevent excessive pull on the lower facial structures.

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Meige's Syndrome

Joanna B. D'Elia and Andrew Blitzler

Meige's syndrome is a type of adult-onset dystonia that was first described by Henry Meige in 1910. Primary Meige's syndrome is characterized by a combination of oromandibular dystonia (OMD) and idiopathic or essential blepharospasm. Secondary Meige's syndrome can be encountered in the context of several different neurodegenerative disorders, in the chronic administration of neuroleptics, and in patients with focal brain lesions. These secondary cases suggest that dysfunction of the basal ganglia or of the mesencephalic/diencephalic region plays an important role in this syndrome.¹

The pathophysiology of this syndrome, like all segmental dystonias, is not well understood. Various hypotheses have been formulated, although none has been universally accepted. A recent study using functional magnetic resonance imaging (MRI) showed reduced

activation of the primary motor and ventral precortex during involuntary oromandibular movements, a phenomenon that probably reflects reduced cortical inhibition in motor and premotor areas. The same study revealed an increased activation of the somatosensory areas, which indicates that an altered somatosensory representation may be responsible for the manifestations of this syndrome.²

The onset of symptoms typically occurs between 30 and 70 years of age, most often in the sixth decade. It is twice as common in women as in men. In most cases, the involuntary facial and mandible movements gradually progress in intensity, as well as in the number of affected muscle groups, over a period of 1 to 4 years after onset, after which they usually stabilize. The orofacial contractions are bilateral, symmetric, and nonrhythmic spasms of various

muscle groups. They typically last from a few seconds to minutes and can be triggered by certain actions, and especially by psychosocial stressors.

In order of decreasing frequency the following types of spasms may be seen: eye closure (blepharospasm), mouth retraction, eyebrow elevation and frowning, platysmal contractions, neck spasms (flexion, extension, and lateral rotation), jaw-opening spasms, soft palate spasms, mouth-clenching spasms, lip pursing, inspiratory spasms, lip-tightening spasms, contraction of nasal and floor-of-mouth muscles, spasms of tongue protrusion, and spasms of shoulder elevation. Several types of orbicularis oculi spasms occur in Meige's syndrome: brief clonic spasms, prolonged dystonic spasms, constant tonic contraction, and "apraxia" of lid opening.³

Historically, these spasms were considered psychogenic in origin and patients were prescribed psychiatric treatment. Even after recognition of the neurologic basis of segmental dystonias, medical therapy with various agents has historically been the first-line treatment. Such agents as dopaminergic/anticholinergics, tetrabenazine, benzodiazepines, and baclofen have been used with varying success. Botulinum neurotoxin (BoNT) injections with electromyography (EMG) guidance in selected muscles have also been used successfully to control the spasms associated with this syndrome. Corrective ablative surgery (eyelid myectomy, blepharoplasty, and lid lifts) has been described, but due to lack of convincing efficacy data, it currently plays little, if any, role in therapy. Globus pal-

lidus deep brain stimulation (DBS) is an established treatment for medically refractory primary forms of dystonia. Given the dramatic clinical improvement seen in DBS patients with primary generalized dystonia, trials of pallidal DBS have been performed for the treatment of segmental dystonia as well.⁴

■ Workup

A comprehensive history and physical examination focusing on the ophthalmologic, otolaryngologic, and neurologic areas should be performed. During the history taking, the patient should be questioned about the presence of any other neurologic symptoms; a family history of neurologic disorders and a thorough medication history should be obtained. The spasms associated with Meige's syndrome may lead to eye irritation, decreased visual acuity, xerostomia, dysarthria, and dysphagia. The physician should specifically ask the patient about the presence of any of these symptoms. The examination should focus on identifying the specific musculature that is affected by the spasms. Precise identification of affected muscles is essential for satisfactory treatment. Ideally this identification should not only consist of subjective assessment, but also include video recordings of the face as well as EMG of the orbicularis oris, orbicularis oculi, temporalis, masseter, digastrics, and pterygoids as indicated.

A neurologist (preferably a specialist in movement disorders) should be

consulted for any patient suspected of having Meige's syndrome. This consultation may facilitate identifying additional neurologic symptoms outside of the head and neck region as well as initiate a discussion regarding an appropriate oral medication regimen. An ophthalmologist should also be consulted to properly establish a baseline of visual function and determine whether or not the patient requires ophthalmologic treatment. In addition, if the patient's condition has affected his or her dental health, consideration should be given to consulting a dentist specializing in oral physiology.⁵

■ Anatomy

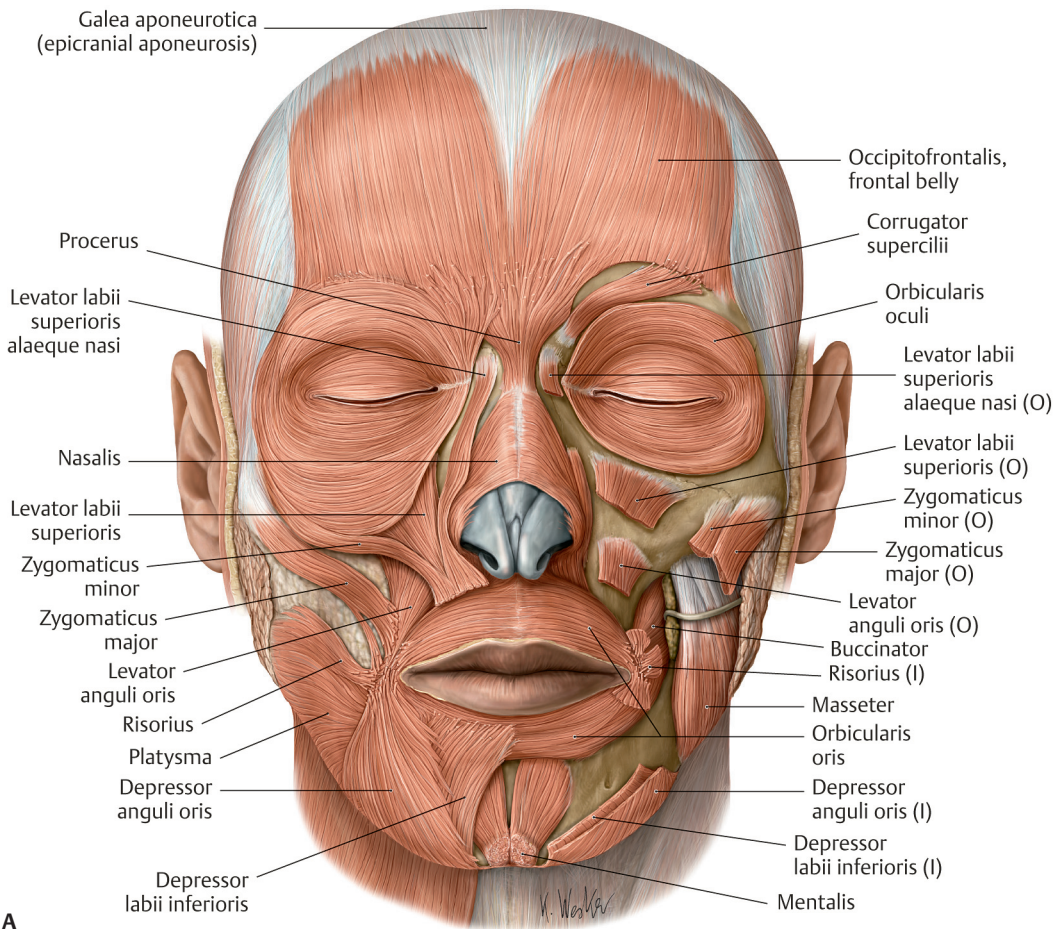
The anatomy of the musculature typically affected by oromandibular dystonia (masseter, temporalis, pterygoids) is reviewed in Chapter 5. Similarly, the anatomy relevant to the treatment of blepharospasm is reviewed in Chapter 2 and consequently will not be discussed in this chapter.

The platysma muscle takes the shape of a broad sheet arising from the fascia covering the upper portion of the pectoralis major and deltoid muscle. The fibers cross the clavicle and spread obliquely and medially.

The depressor anguli oris muscle arises from the oblique line of the mandible and inserts via a narrow fasciculus into the corner of the mouth. At its origin it is continuous with the platysma, whereas at its insertion it is continuous with the orbicularis oris and risorius (**Fig. 4.1**).

■ Technique

For patients with platysmal spasm, one therapeutic option is to inject this muscle using BoNT. The anterior and posterior borders of the platysma should be identified and marked. Horizontal lines spanning the width of the muscle should be drawn, approximately 2 cm apart until the bottom of the platysma is reached. Typically three or four injection sites are utilized. A 27-gauge, hollow-bore monopolar EMG needle is passed through the skin starting at the anterior edge of the horizontal line until the muscle fibers are pierced. The needle is then oriented parallel to the skin and directed posteriorly toward the opposite end of the line. The desired dose is then delivered throughout the muscle pass as the needle is withdrawn. Each pass should deliver 2.5 to 5.0 units (U), with the dose range equaling 7.5 to 20 U per side (**Fig. 4.2**). Alternatively, the patient can be instructed to activate the platysma muscle,



A

Fig. 4.1 (A) Anatomy of the depressor anguli oris and platysma muscles. (From Atlas of Anatomy, © Thieme 2008, Illustration by Karl Wesker.) (continued on next page)

and each vertically oriented band can be injected directly, with an identical dose as described previously (**Fig. 4.3**).

The depressor anguli oris (DAO) can be located by identifying a point 7 mm

lateral and 7 mm inferior to the oral commissure. An injection of 2 to 4 U of toxin at this coordinate under EMG guidance should reliably treat spasm of the DAO muscle⁶ (**Fig. 4.4**).

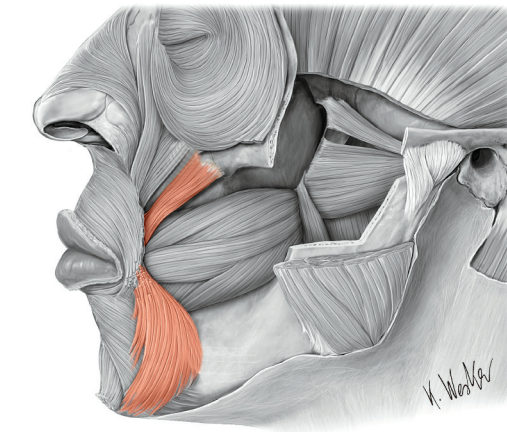
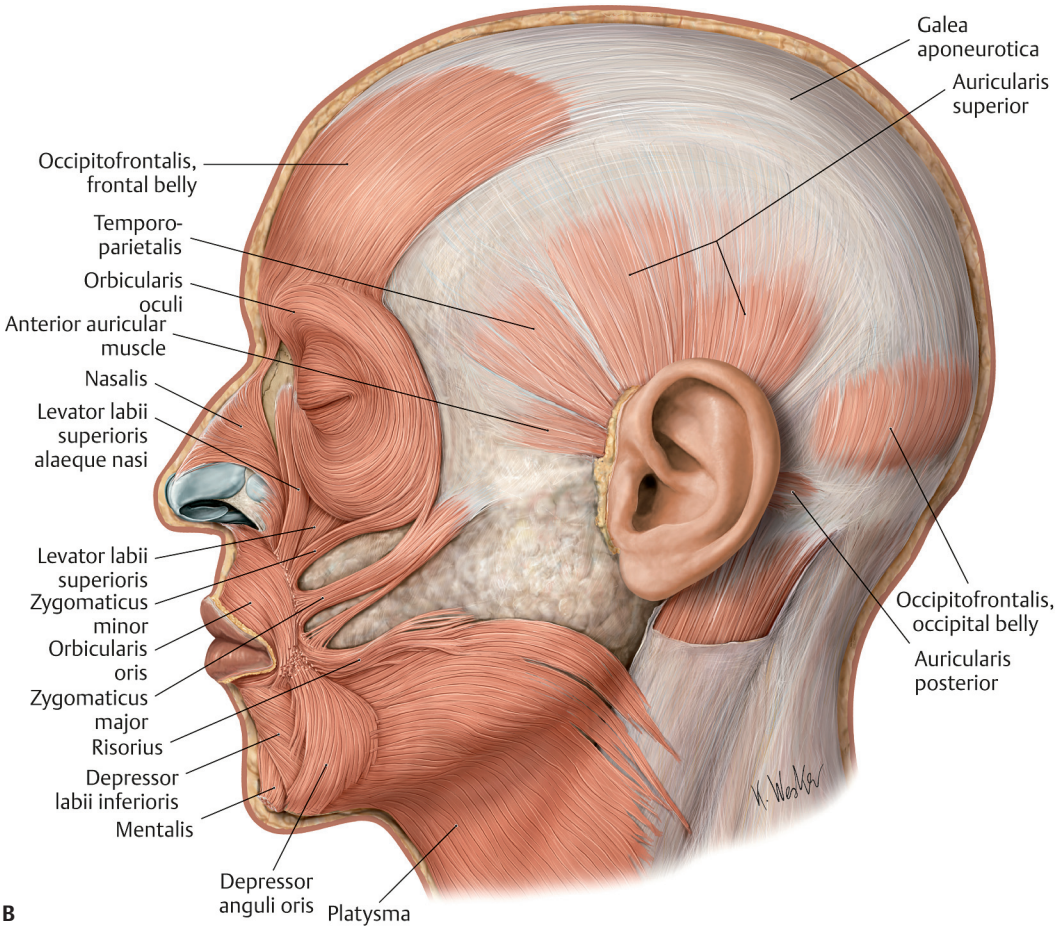


Fig. 4.1 (B,C) (Continued)

Fig. 4.2 Platysma injection technique.

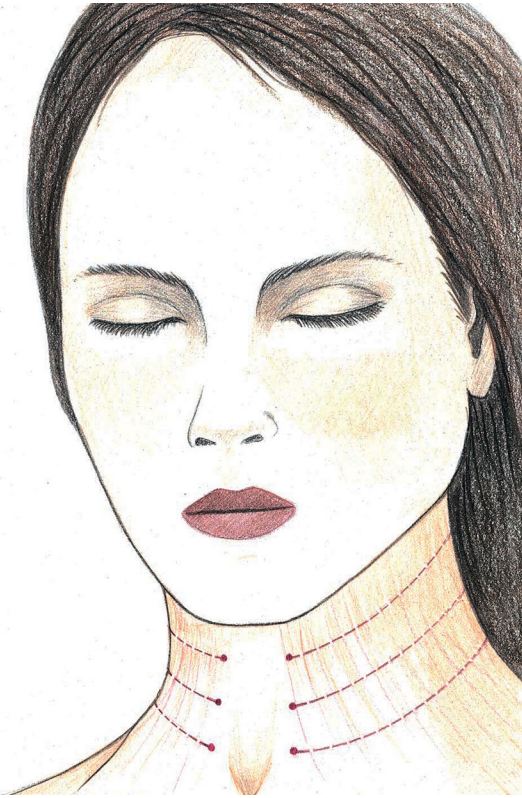


Fig. 4.3 Injection of the vertical platysma bands.



Fig. 4.4 Injection of the depressor anguli oris muscle.

■ Follow-Up

Patients should be examined at 2 weeks postinjection for assessment of the location and dose of the injection. The dose may be adjusted according to the satisfaction level of the patient and physician.

■ Complications and Pitfalls

Complications of injections for the muscles of mastication and orbicularis oculi are discussed in Chapters 5 and 2, respectively.

Side effects of DAO injection may include asymmetric smile and labial in-

competence. Diffusion of BoNT during platysmal injection to the infrahyoid strap muscles could lead to dysphagia. Such complications are always possible but are minimized when using EMG for precise location of the injection site and the minimum amount of toxin necessary to achieve the desired effect.

■ Conclusion

Electromyography-guided botulinum neurotoxin is a safe and effective treatment for temporary amelioration of the dystonic movements associated with Meige's syndrome.



Video 3 Meige's Syndrome (Multicranial Dystonia)

Notice the patient's excessive blinking, pulling of lower facial muscles, platysma, and anterior neck. He also has intermittent dysarthria.

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Oromandibular Dystonia

Daniel Novakovic and Ajay E. Chitkara

Oromandibular dystonia (OMD) is a neurologic disorder affecting both males and females with onset primarily in the fifth and sixth decades of life. It is characterized by repetitive, involuntary, patterned contractions or spasms of the masticatory, lingual, and perioral musculature. Typically the dystonic movements are action induced and can impair speech, mastication, and swallowing, and cause significant social embarrassment. OMD is a subset of cranial-cervical dystonias, and when the symptoms of OMD are coupled with blepharospasm, the condition is known as Meige's syndrome. Like other focal dystonias, it is usually a primary condition thought to be related to an underlying disorder of the basal ganglia. However, it may also occur as a result of secondary causes such as drug exposure, Wilson's disease, and peripheral injury such as dental procedures.¹⁻³

Oromandibular dystonia may be classified as jaw opening, jaw closing, jaw deviation, and tongue protrusion sub-

types, with most cases representing a combination of these subtypes. Perioral movements (depressor anguli oris [DAO], platysma) and head turning (sternocleidomastoid muscle [SCM]) may also be associated, but it is not clear whether they are compensatory to the OMD or part of a more complex multifocal dystonia such as Meige's syndrome.

■ Workup

Patients should be evaluated for a family history of dystonia or the presence of other dystonias. A detailed drug and psychiatric history is also very important to exclude the possibility of tardive dystonia secondary to dopaminergic antagonists or neuroleptic drugs.¹

Some OMDs may be alleviated by a sensory trick,⁴ or *geste antagonistique*, such as singing, chewing on a toothpick, placing an olive pit into the gingivobuccal sulcus, or scratching the chin. These

sensory tricks afford only temporary symptomatic relief.

Oral agents remain one of the first-line medical treatments for OMD, and evaluation by a neurologist for consideration of such treatment is a prudent initial step. Botulinum neurotoxin (BoNT) injections can also be used to reduce or eliminate involuntary movements and are well established as a treatment since their first description by Brin and Blitzer^{5,6} in 1987. Patients with jaw-closing OMD tend to respond better than patients with the other types of movements. Imaging may reveal evidence of prior head trauma or basal ganglia abnormality. Blood tests are not routinely performed prior to initiation of BoNT therapy, although low serum ceruloplasmin and certain genetic markers may be consistent with the diagnosis of dystonia.

■ Selection of Treatment Areas/Anatomy

Jaw Deviation/Protrusion

Involuntary spasms of the external (lateral) pterygoid muscles are responsible for jaw-deviation and jaw-protrusion movements. Treatment of these OMD movements begins with injecting the external pterygoids. This muscle consists of two heads; the superior head originates on the greater wing of the sphenoid bone, and the inferior head originates on the lateral surface of the lateral pterygoid plate and runs posterolateral. The superior and inferior heads converge to insert into the medial as-

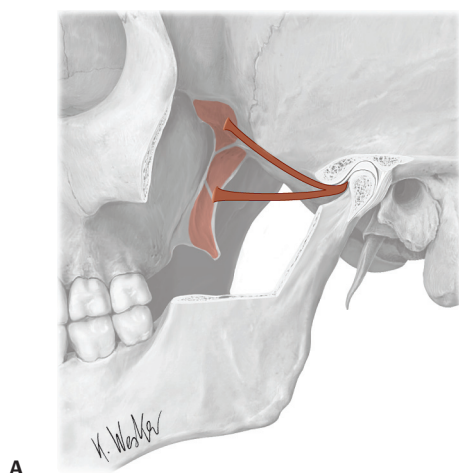
pect of the condylar process of the mandible (**Fig. 5.1**). Unilateral action of these muscles causes lateral jaw excursion to the contralateral side. Bilateral action of these muscles causes jaw protrusion or jaw opening. The internal (medial) pterygoids are primarily jaw closers but can work with the external pterygoids in jaw deviation (**Fig. 5.2**).

Jaw Closing

Involuntary actions of the masseter, temporalis, and internal or medial pterygoid muscles are responsible for jaw-closing OMD movements (**Fig. 5.3**). Initial treatment involves injecting the masseter and temporalis muscles first and adding treatment of the internal pterygoid for nonresponsive cases or suboptimal results.

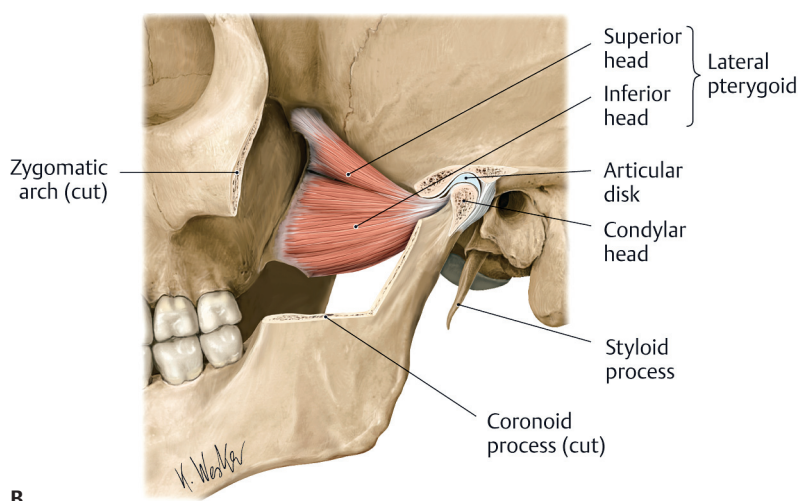
The masseter originates from the anterior two thirds of the zygomatic arch and the zygomatic process of the maxilla. It inserts on the inferior and lateral surface of the angle and lower ramus of the mandible (**Fig. 5.4**). The internal (or medial) pterygoid originates from the medial surface of the lateral pterygoid plate, pyramidal process of palatine bone, and maxillary tuberosity. It inserts on the medial angle of the mandible, forming a U-shaped sling around the inferior mandible border with the masseter. These two muscles elevate the mandible, enabling forced closure of the mouth.

The temporalis muscle is a broad fan-shaped muscle originating from the temporal lines on the parietal bone of the skull and inserting into the coronoid process of the mandible after passing



A

Fig. 5.1 (A,B) External (lateral) pterygoid muscle. (From Atlas of Anatomy, © Thieme 2008, Illustration by Karl Wesker.)



B

medial to the zygomatic arch. It is covered by a strong thick fascia that can be felt as resistance when administering injections. It elevates and retracts the mandible (**Fig. 5.5**).

The jaw-closing muscles are characterized by larger masses of contractile tissue⁷ compared with the jaw-opening muscles and accordingly require larger doses of BoNT. They respond better to BoNT treatment compared with the jaw-opening OMDs.⁸

Jaw Opening/Tongue Movements

The OMDs of jaw opening are mostly due to involuntary movements of the submental muscles (digastrics, genio-glossus, geniohyoid, mylohyoid, hyoglossus) and the external pterygoids (**Fig. 5.6**). The platysma can also function as a jaw opener, and its treatment is addressed in another chapter.

The digastric muscle has two bellies that insert into an intermediate tendon

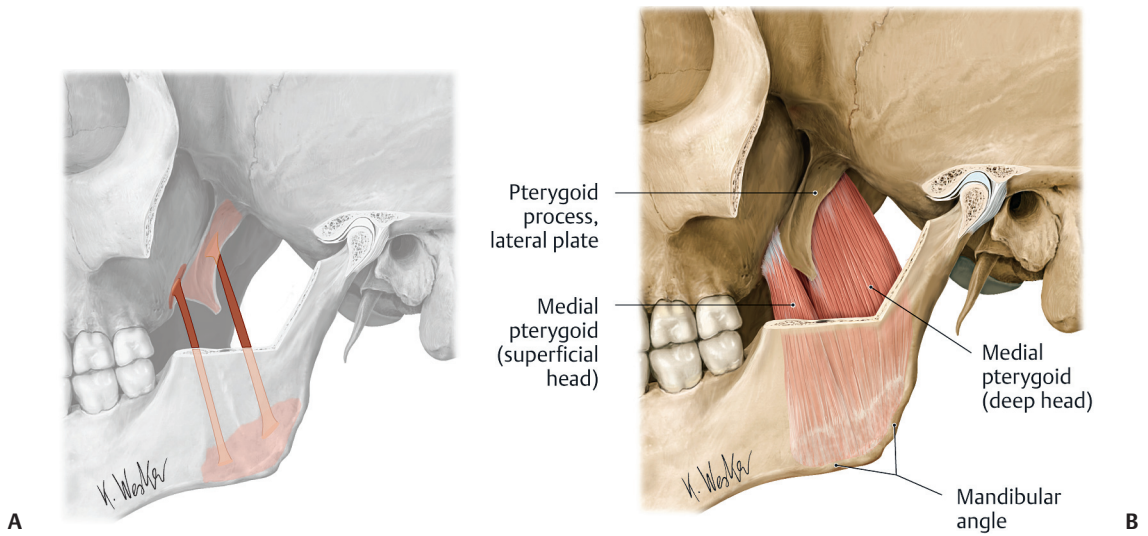


Fig. 5.2 (A,B) Internal (medial) pterygoid muscle. (From Atlas of Anatomy, © Thieme 2008, Illustration by Karl Wesker.)

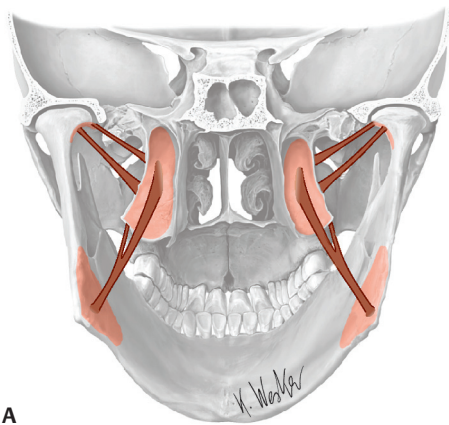


Fig. 5.3 (A,B) Muscles of mastication. (From Atlas of Anatomy, © Thieme 2008, Illustration by Karl Wesker.)

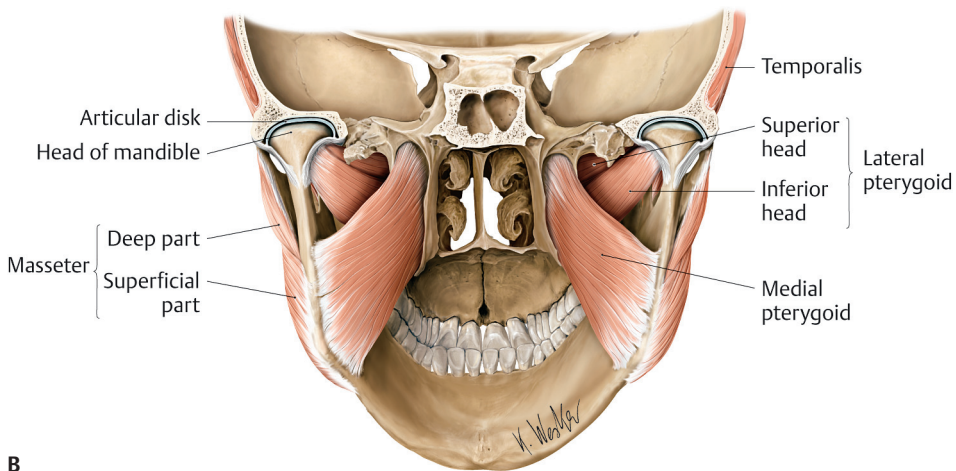


Fig. 5.4 (A,B) Masseter muscle. (From Atlas of Anatomy, © Thieme 2008, Illustration by Karl Wesker.)

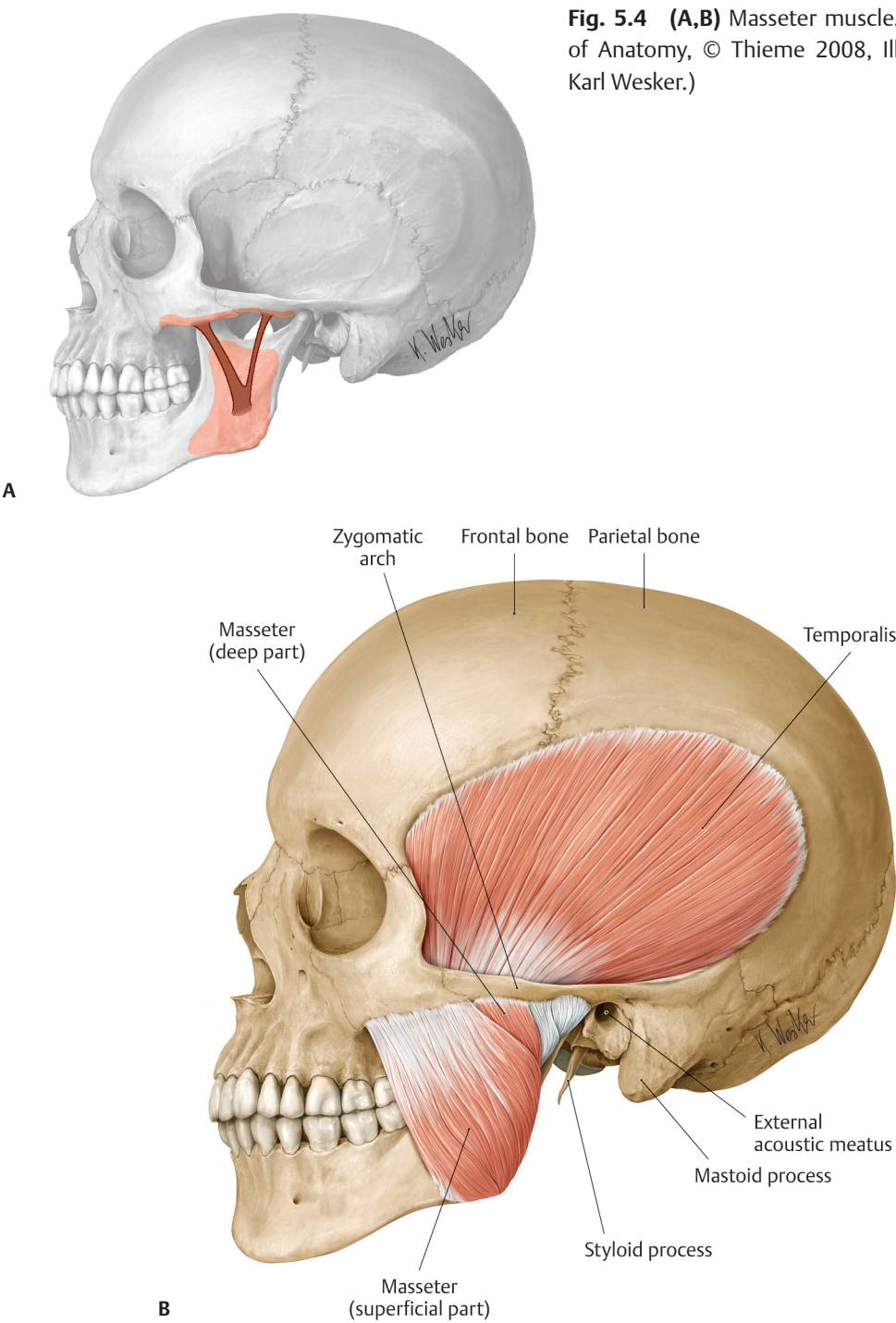
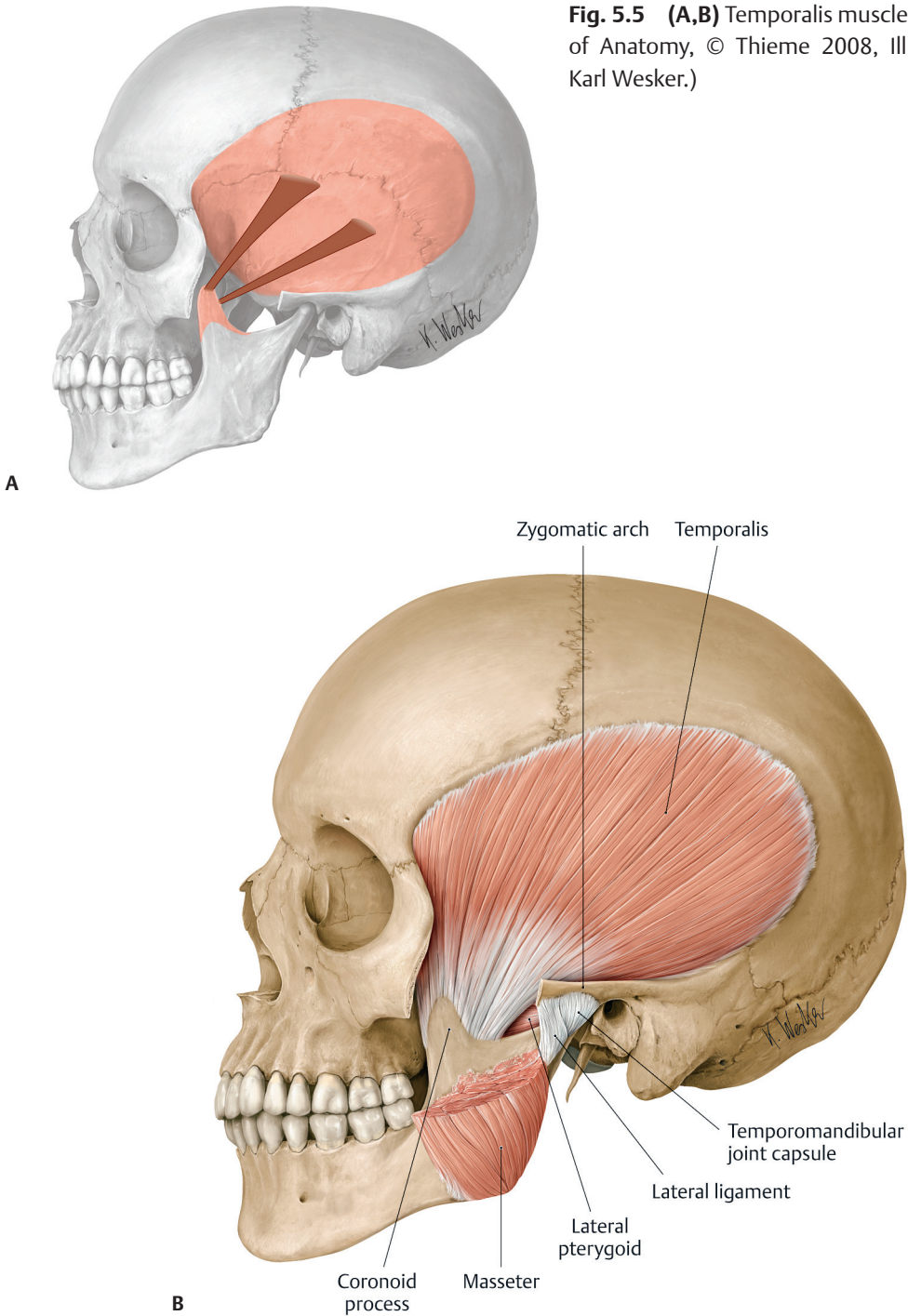


Fig. 5.5 (A,B) Temporalis muscle. (From Atlas of Anatomy, © Thieme 2008, Illustration by Karl Wesker.)



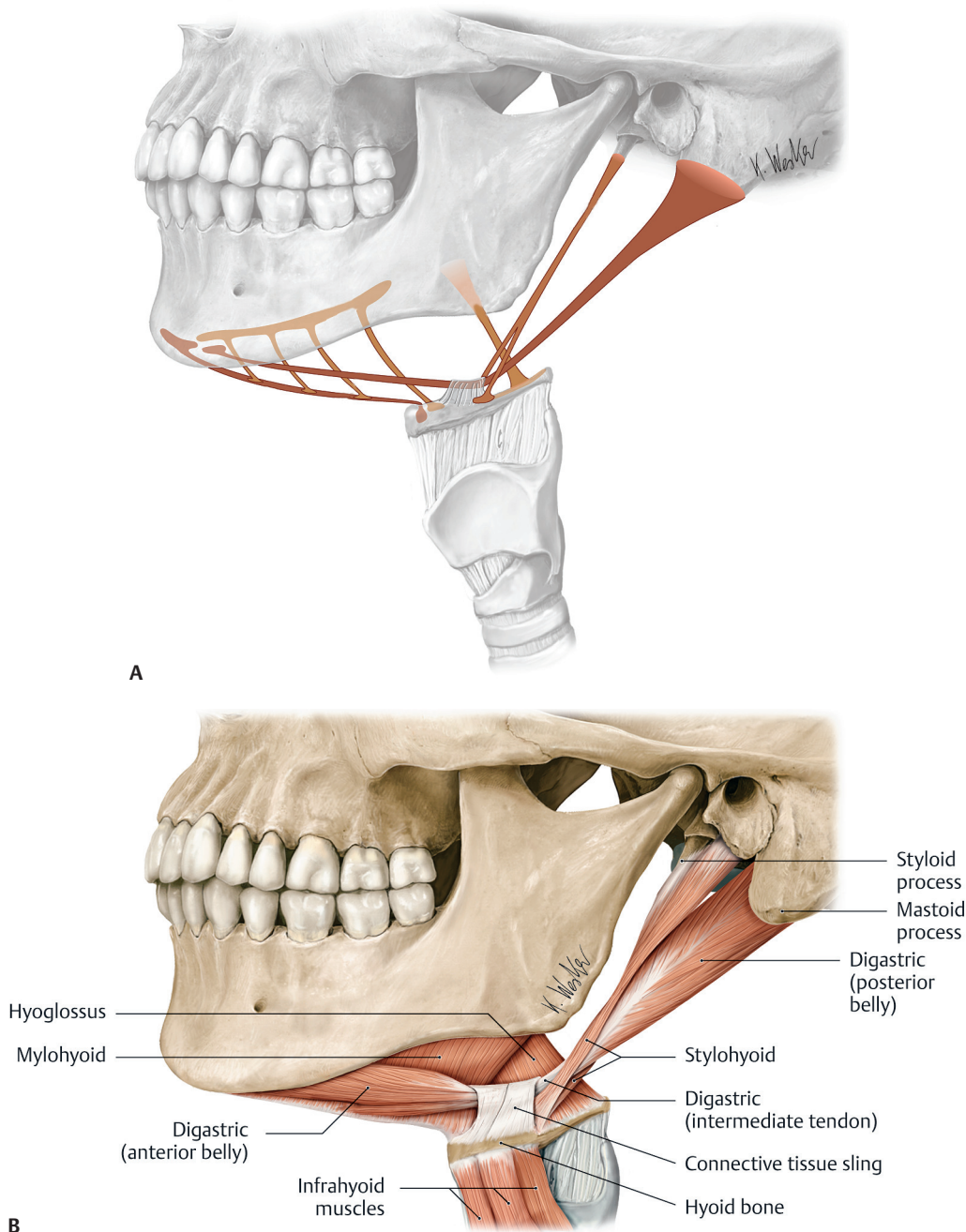


Fig. 5.6 (A,B) Muscles of the oral floor. (From Atlas of Anatomy, © Thieme 2008, Illustration by Karl Wesker.)

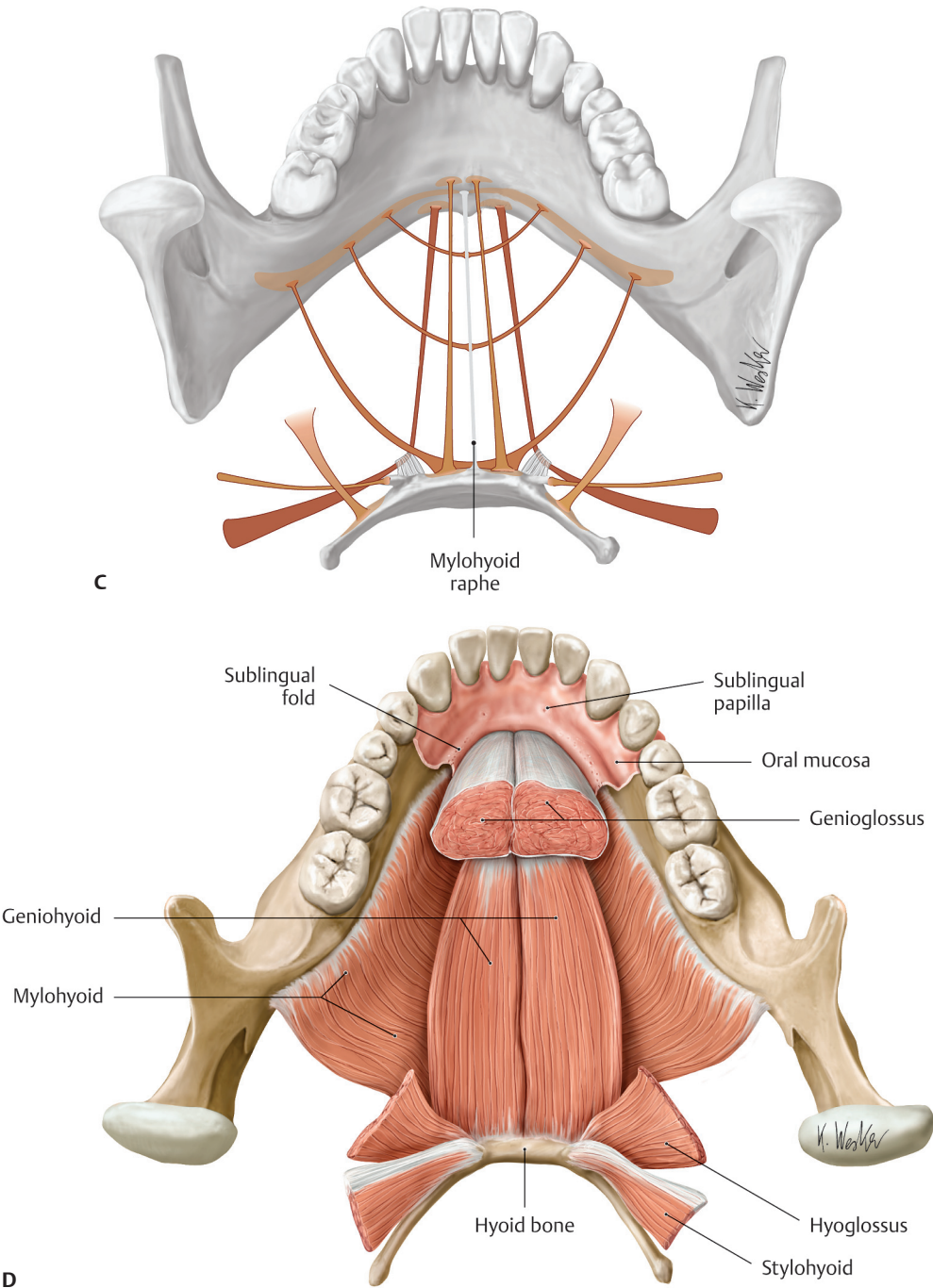


Fig. 5.6 (C,D) (Continued)

on the greater horn of the hyoid bone. The anterior belly originates from the digastric fossa on the anterior internal mandible, and the posterior belly originates on the mastoid process of the temporal bone. The muscles open the jaw when the temporalis and masseter are relaxed.

The genioglossus, geniohyoid, mylohyoid, and hyoglossus have lesser effects on jaw opening, but all assist in tongue movement and deglutition. Treatment of these muscles can be very challenging due to the high risk of dysphagia and dysarthria (over 10%) due to overinjection, diffusion, or inaccurate needle placement. The normal flaccid paresis from the BoNT also can cause undesirable effects on mastication and speech.

Tongue Movements

Tongue movements in OMD may be due primarily to extrinsic or intrinsic tongue musculature involvement or secondarily to movements of the jaw. Tongue protrusion movements are the most common and most symptomatic for the patient. When OMD results predominantly in tongue protrusion, treatment with BoNT injections into the genioglossus muscles (**Fig. 5.7**) can improve symptoms in two thirds of patients with approximately a 15% rate of mild dysphagia.⁹ These injections should be utilized cautiously in select cases when lingual protrusion as part of OMD persists despite treatment of jaw movements. The high risk of dysphagia and

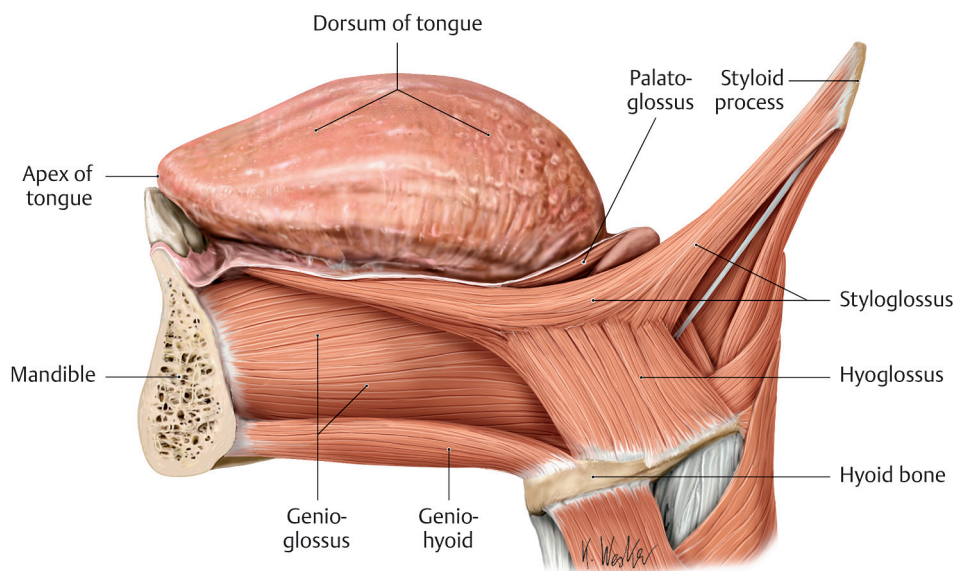


Fig. 5.7 Muscles of the tongue. (From Atlas of Anatomy, © Thieme 2008, Illustration by Karl Wesker.)

the potential for nasogastric or gastrostomy tube placement secondary to genioglossal chemodenervation¹⁰ preclude the routine use of these injections.

■ Technique

Patients are seated comfortably in a procedure chair. All injections are complemented with electromyographic (EMG) guidance. Ground and reference electrodes are placed over the SCM in the neck. Local anesthesia is not routinely used. Injections are performed using a hollow, 27-gauge, 37-mm-long, Teflon-coated, monopolar EMG needle placed on a 1-mL tuberculin syringe. The areas of skin overlying the muscles to be treated

are prepared using alcohol. To minimize the risk of contamination, the intraoral injections are administered last.

Masseter

A dilution of 5 units (U) per 0.1 mL of onabotulinumtoxinA is used for the masseter. The muscle belly can be palpated prior to injection by asking the patient to clench the teeth. The needle is placed through the skin into the muscle, and the position is confirmed by listening for brisk EMG activity while the patient clenches his or her teeth (**Fig. 5.8**). The procedure is repeated on the contralateral side. A nearly perpendicular injection angle is used to deliver 0.1-mL aliquots at three or four sites in the muscle.

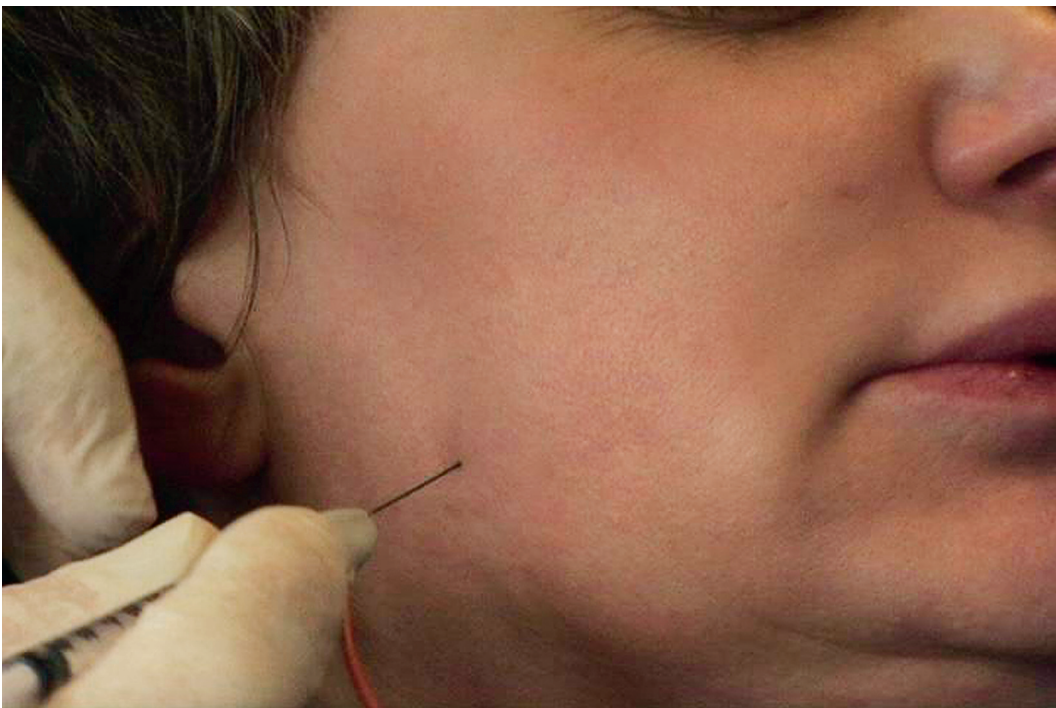


Fig. 5.8 Masseter muscle injection.



Fig. 5.9 Temporalis muscle injection.

Prior to withdrawing the needle from the skin, injections are dispersed within the muscle by changing the depth and angle of the needle. The injections are spaced approximately 1 cm apart within the muscle.

Temporalis

A dilution of 5 U per 0.1 mL of onabotulinumtoxinA is used for the temporalis muscle. The muscle belly and temporal line are palpated while the patient clenches his or her teeth. The needle is placed through the skin overlying the temporalis muscle and position is confirmed with the brisk EMG activity that occurs with the patient's teeth clenching. To enhance the accuracy of the injection into the thin temporalis muscle, the needle is usually inserted along the

anterior or superior border of the temporalis muscle, and subsequently advanced posteriorly or inferiorly in the sagittal plane, once the correct depth of the needle placement is confirmed with the EMG (**Fig. 5.9**). This allows multiple aliquots to be injected with one pass of the needle, a technique that is impossible if the needle is passed in a lateral to medial direction. Using the previously described technique, 0.1 mL aliquots are delivered at four or five points within the temporalis muscle. These aliquots are spaced at 1-cm intervals, preferably through one to three skin puncture sites.

Anterior Digastric Belly

A dilution of 5 U per 0.1 mL of onabotulinumtoxinA is used. The neck is extended and the patient is asked to open



Fig. 5.10 External pterygoid muscle injection.

the jaw widely to allow palpation of the anterior digastric muscle belly. The needle is placed through the skin into the muscle closer to the mentum than to the hyoid to minimize dysphagia. Position is confirmed by brisk EMG activity on mouth opening, and 0.1 mL aliquots are injected at multiple sites. The procedure is repeated on the contralateral side.

External Pterygoid

There are two approaches for treatment of the external pterygoid muscle. The extra-oral cutaneous approach is introduced between the two heads of the mandible. Because this approach is perpendicular to the muscle, it can be less reliable and does not allow for multiple injection points. The intra-oral approach allows for better distribution of the toxin

along the muscle (**Fig. 5.10**). The clinician uses a headlight for intraoral visualization, and the patient is asked to open the mouth fully. The clinician's index finger is used to retract the cheek laterally, and then the patient is asked to close the mouth just slightly while the external pterygoid plate is palpated posterolateral to the last upper molar and medial to the ramus of the mandible. The needle is angled approximately 20 degrees superiorly and laterally and advanced in the long axis of the muscle. Correct placement is confirmed by asking the patient to move the jaw side to side until sharp EMG activity is heard. OnabotulinumtoxinA is injected at two or three points along this axis, advancing the needle and confirming the position in the muscle with EMG recruitment prior to each injection. The same

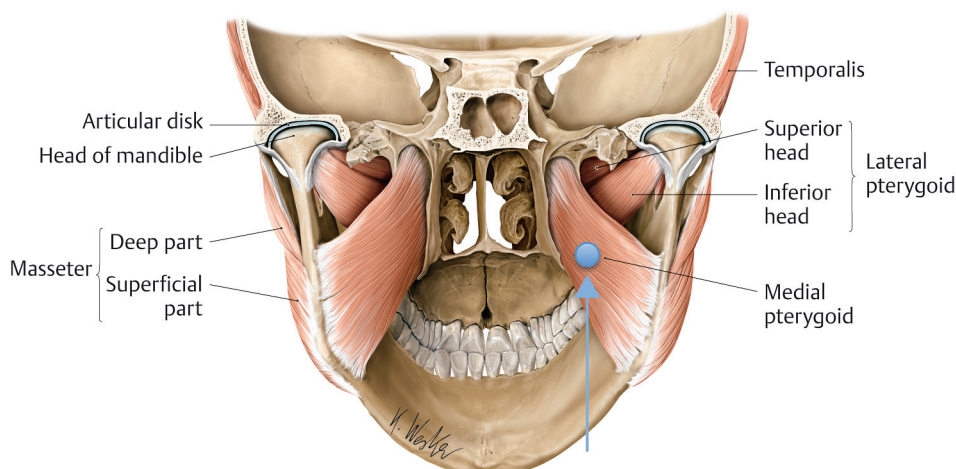


Fig. 5.11 Internal pterygoid muscle injection. Blue arrow = injection needle trajectory; blue circle = injection site. (From Atlas of Anatomy, © Thieme 2008, Illustration by Karl Wesker.)

procedure is repeated on the contralateral side. Dosing starts at 10 U of onabotulinumtoxinA per muscle, and can be altered according to treatment response. For an asymmetric jaw swing, differential dosing can be employed with and extra 5 to 10 U given in the more active muscle (opposite to the direction of jaw swing).

Internal Pterygoid

The internal pterygoid is not routinely injected as a first-line muscle for OMD but rather is added to the treatment regimen for patients with an inadequate response. OnabotulinumtoxinA is diluted to 5 U per 0.1 mL. The needle is placed through the skin in the submandibular area and directed superiorly deep to the mandible and the U-shaped sling, which the masseter forms with the internal pterygoid, and along the inner aspect of the mandibular ramus, thus entering the

muscle (**Fig. 5.11**). The position is confirmed by brisk EMG activity when the patient is asked to clench, and the muscle is injected at two to three points. The same procedure is performed on the contralateral side. Rarely, the facial artery, internal maxillary artery, or arterial branches may be encountered during these injections.

■ Follow-Up

The response to the initial treatment is monitored by clinical assessment at the 3-week mark. Patients are questioned about persistent symptoms and side effects. Repeat observation facilitates targeting muscle groups that need further treatment. Asymmetric movements are also assessed at this point, and some muscle groups may require further unilateral treatment. The dosing of top-up treatments is assessed individually but

typically is lower than that of the initial treatment. Subsequent treatments are at the patient's discretion; the average patient returns every 3 to 4 months. Dosing is adjusted according to the side-effect profile and the length of effect, and the patient is asked to call 3 weeks after the treatment to report any side effects, undesired effects, or inadequate response.

■ Complications and Pitfalls

Patients are extensively counseled prior to treatment about the potential risks of excessive toxin dosing, inaccurate needle placement, or toxin diffusion. The most common side effect is weakness of mastication. Long-term side effects of treatment may include temporalis and masseter hypofunctional atrophy with associated changes in facial morphology. Rare complications due to inaccurate needle placement or diffusion include dysphagia and dysarthria (hyoid and tongue musculature) or perioral incompetence and facial asymmetry (facial musculature). These are always self-limiting and they resolve within 3 months, but may have significant im-

pact upon the patient's quality of life. Development of severe dysphagia does occur¹¹ and may require feeding with a nasogastric tube until the effects of the treatment subside.

■ Conclusion

Oromandibular dystonia can involve isolated or multiple muscle groups of the face and neck. The dystonic contractions often cause functional and social challenges to the patients. Treatment with BoNT can help alleviate the hyperfunctional contractions and improve the individual's quality of life. Given the complex, dynamic oromandibular musculature, which is involved in chewing and speaking, the treatment of these muscles can often adversely affect the desired normal function of the target muscle groups. Successful treatment often hinges upon selectively treating the most affected muscles, and titrating the dose of BoNT for the greatest benefit with the least amount of undesired or adverse effects. Complementary management with oral medications often ameliorates the overall symptomatology.



Oromandibular Dystonia

Most oromandibular dystonia (OMD) is related to closing symptoms. The injection of the masseter and temporalis muscles can be seen in Video 18. The opening type of OMD is usually treated with injections of the external pterygoid muscles, also seen in Video 18. Occasionally the anterior belly of the digastric muscles is injected under the mentum close to the chin, in order to prevent diffusion to the tongue base and consequent dysphagia.

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Spasmodic Dysphonia

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The therapeutic application of botulinum neurotoxin (BoNT) into the larynx for spasmodic dysphonia has been in clinical practice for over two decades and is the current gold standard of treatment. It has been called the primary therapy for spasmodic dysphonia by the American Academy of Otolaryngology–Head and Neck Surgery (Policy Statement: Botulinum Toxin; reaffirmed March 1, 1999). This chapter reviews the options for diagnosis and treatment of spasmodic dysphonia, with particular attention to treatment with BoNT.

■ Background and History

Spasmodic dysphonia is a clinical syndrome characterized by involuntary, hyperfunctional spasms or postures of the internal laryngeal musculature, producing abnormal speech. Traube¹ first used

the term *spastic dysphonia* to describe patients with nervous hoarseness in 1871. Historically, the terms *spastic dysphonia*, *aspartic aphonia*, *phonic laryngeal spasm*, and *coordinated laryngeal spasm* have been used to describe the same clinical presentation.^{2,3} Long thought to be psychological, spasmodic dysphonia was shown to be clearly organic and neurologic in nature by the dramatic response to nerve section in pioneering work by Dedo and Behlau.⁴ In 1982, Mardsen and Sheehy⁵ recognized the underlying pathology to be dystonia. They noted that “all evidence points to the conclusion that blepharospasm and oromandibular dystonia seen in Meige disease is another manifestation of adult-onset torsion dystonia, [and] since dysphonia may occur in the same syndrome, it is quite likely that dysphonia itself may be the sole manifestation of dystonia.” In 1988, Blitzer and colleagues⁶ used

clinical examination and laryngeal electromyography to prove that most cases of spastic dysphonia actually represented focal cranial dystonias.

■ Classification and Presentation

Spasmodic dysphonia is classified as a laryngeal dystonia, a clinical term used to describe an action-induced, task-specific, laryngeal neuromuscular disorder.⁷ Dystonias are classified by clinical symptom, age at onset, distribution, and cause. When classified by distribution, dystonias are categorized as focal, segmental, multifocal, or generalized. Spasmodic dysphonia is a focal dystonia involving the laryngeal adductor muscles (lateral cricoarytenoid, interarytenoid, thyroarytenoid, and possibly the cricothyroid), abductor muscles (posterior cricoarytenoid), or both, with occasional involvement of supraglottic structures. There appears to be variability in the degree and topography of laryngeal muscle involvement, and the type of laryngeal dystonia seen clinically may actually represent a predominance of either adductor or abductor activity.⁸

The majority of dystonias are primary, or of idiopathic etiology. These patients have a normal perinatal and early developmental history; no prior history of head trauma or neurologic illness; no exposure to drugs known to cause acquired dystonia (e.g., phenothiazines); and normal intellectual, pyramidal, cerebellar, and sensory examinations. Identification of any cause by history, examination, or

laboratory studies defines secondary dystonia. Most cases of spasmodic dysphonia present as focal laryngeal dystonias. A small number of these cases may be associated with or progress to symptoms in another part of the body. Although in our experience this is a small percentage, rates as high as 17% have been reported.⁷ Multiple factors have been noted to cause secondary spasmodic dystonia (**Table 6.1**). These may include neurologic disorders, drug exposures, and parkinsonism.

Spasmodic dysphonia can be further divided into abductor and adductor dysphonia. In adductor spasmodic dysphonia, patients present with a choked, strain-strangled voice, breaks in phonation, diminished volume, and a monotonal pitch. Patients with the abductor type present with a breathy, effortful voice, abrupt breaks in fluency, and whispered elements of speech. With severe spasms, patients may be aphonic. Compensatory behaviors may mask the patient's true voice pattern. Patients with a severe adductor spasmodic dysphonia may exhibit compensatory abductor voicing, with aphonia or whispering.⁹ Some authors believe that all patients with spasmodic dysphonia have abductor and adductor contributions, with symptoms manifesting according to the predominant type.^{10,11}

In both groups, patients may demonstrate a phonation-associated tremor. In contrast to essential tremor, the spasmodic dysphonia-associated tremor is irregular and may be secondary to posturing of dystonic muscles in a position in which the agonist contractions do not

Table 6.1 Etiologies of Dystonia

Primary
<i>With hereditary pattern</i> Autosomal dominant
<i>Classic types</i> Childhood onset dystonia Focal dystonia
<i>Variant types</i> Dopa-responsive dystonia Myoclonic dystonia X-linked recessive
<i>Sporadic (without a documented hereditary pattern)</i> Classic types Variant types
Secondary
Associated with other hereditary neurologic disorders, e.g., Wilson’s disease, Huntington’s disease, ceroid lipofuscinosis Environmental, e.g., posttraumatic, postinfectious, vascular, tumor, toxic, phenothiazines (tardive) Dystonia associated with parkinsonism Psychogenic

fully neutralize those of the antagonist muscles. Blitzer and colleagues¹² showed that 25% of spasmodic dysphonia patients may have such a tremor.

■ **Diagnosis and Investigation**

The diagnosis of spasmodic dysphonia is based on perceptual analysis of the voice with a characteristic pattern of vocal spasms, the absence of secondary causes, normal peripheral nerve supply, and intact swallowing and breathing functions of the larynx. Evaluation should include a detailed head and neck and neurologic examination, with particular attention paid to spasm, dysfunction, or tremor in any area of the head and neck. This examination should include flexible laryngoscopy with particular attention to

glottal function for vowel sounds, disruptions, spasms, breathy breaks, and tremor with connected speech segments. We prefer flexible laryngoscopy to the rigid telescope because the larynx is positioned in a more neutral natural posture during the examination. This allows for a fuller assessment of extrinsic muscle hyperfunction, tremor, and dystonic movements during speech. The rigid telescope still has improved magnification and light for the detailed evaluation of the vibratory margin of the vocal fold, and has an appropriate place in the evaluation to exclude mucosal wave pathology. Leonard and Kendall¹³ noted that motion abnormalities in spasmodic dysphonia were present only during specific speaking actions, whereas they were present at all times with muscle tension dysphonia.

The recognition of intermittent hyperfunctional breaks and spasms, with excessive and inappropriate adduction or abduction of the vocal folds during specific vocal tasks, is the basis for the diagnosis of spasmodic dysphonia. The spasms and breaks have a characteristic and reproducible pattern that can be elicited using a standardized set of sentences. During the endoscopic laryngeal exam, adductor-type spasmodic dysphonia should demonstrate intermittent, occasionally more sustained, visible hyperadductory postures with hyperfunctional closure of the true or false vocal folds, excessive medial rotation of the vocalis process, or excessive vocal fold tension that corresponds to the choked, strain-strangled voice breaks. The adductor spasms typically occur with phonation of vowels. The laryngeal exam for abductor-type spasmodic dysphonia should exhibit rapid and hyperfunctional abduction during the breathy voice breaks, which results in a breathy, although effortful, voice quality with aphonic whispered segments. Abductor spasms are marked when trying to phonate a vowel after a voiceless consonant (example /h/, /p/, or /t/). This is in contrast to other causes of a breathy voice such as vocal fold paralysis or presbylarynges, which should give a constant breathy quality to the voice. The diagnosis sometimes can be difficult because of the presence of tremor and overlying functional or compensatory postures that the patient has developed, and a repeat examination after a short course of voice therapy may be useful. The most

effective method for training to recognize spasmodic dysphonia is through repeated exposure to a variety of different voices.

Ludlow and colleagues proposed a three-tier system for the diagnosis of spasmodic dysphonia. Tier one is a screening questionnaire that consists of four questions (**Table 6.2**). Patients are expected to have had symptoms for at least 3 months and answer in the affirmative to the first two questions to be considered as having possible spasmodic dysphonia. Tier two is a clinical speech examination in which patients are taken through a series of vocal exercises by a voice specialist. Specific sentences are used to elicit abductor and adductor voice breaks. Patients are expected to have one or more voice breaks during speaking and fewer during whispering to be included. Tier three, fiberoptic laryngoscopy, reveals normal glottal function with swallowing, whistling, and coughing while demonstrating vocal fold spasm, or tremor while speaking sentences. Using this three-tiered technique on a series of 30 patients with known muscle tension dysphonia, spasmodic dysphonia, or tremor, Ludlow and colleagues¹⁴ were able to correctly categorize 97% of patients.

Objective testing and other diagnostic modalities can be useful in assisting in the diagnosis of difficult cases. In assessing the utility of acoustic analysis, Zwirner and coworkers¹⁵ found significantly higher mean values of standard deviation of fundamental frequency, jitter, shimmer, and voice break factor,

Table 6.2 Screening Questions for Spasmodic Dysphonia³⁸

Question	<i>Usually Expected for Spasmodic Dysphonia</i>	<i>Not Expected for Spasmodic Dysphonia</i>
1. Does it take a lot of work for you to talk?	Yes	No
2. Is it sometimes easier and sometimes more difficult to talk?	Yes	Sometimes normal without treatment
3. How long has it been difficult for you to talk?	3 months or more, a chronic problem	Less than 3 months
4. Can you do any of the following normally?		
Shout	Yes	No
Cry	Yes	No
Laugh	Yes	No
Whisper	Yes	Same as speech
Sing	Yes	More affected than speech
Yawn	Yes	No

and significantly lower mean values of signal-to-noise ratio in spasmodic dysphonia patients when compared with normal controls. Using acoustic analysis, Sapienza and coworkers¹⁶ found that only patients with adductor spasmodic dysphonia manifested voice breaks during speech, specifically with sustained vowels. They also found patients with adductor spasmodic dysphonia to have greater variation in the type of acoustic event produced as a function of speech task. Koufman¹⁷ found spectral analysis to be useful in differentiating adductor spasmodic dysphonia and muscle tension dysphonia (MTD), sometimes a challenging task given the supraglottic hyperfunction that may be present in both processes. Koufman noted that voice breaks were usually present in spasmodic dysphonia but absent in MTD. The spasmodic dysphonia patients also had well-defined formants, whereas the

MTD patients did not, and the MTD patients had excessive high-frequency spectral noise that was minimal in spasmodic dysphonia patients.¹⁷ This showed that spectral analysis, although not a frequently used tool, could potentially be a useful adjunct to differentiate adductor spasmodic dysphonia from muscle tension dysphonia.

Laryngeal electromyography (EMG) is also a potential adjunct in the diagnosis of adductor spasmodic dysphonia. Typically, EMG demonstrates abnormal, but not pathognomonic, large and polyphasic motor unit potentials and an abnormally long latency from the initiation of electrical signal to the beginning of sound production.^{18,19} Nash and Ludlow²⁰ compared laryngeal EMG results in patients with adductor spasmodic dysphonia against controls. They found a significant increase in mean muscle activity during voice breaks in the thy-

roarytenoid muscle, whereas muscle tone in these patients was equivalent to controls during normal speech. Hillel⁸ used laryngeal EMG to examine 11 patients without laryngeal pathology, and then compared these findings with those of 59 patients with abductor, adductor, mixed, and tremor spasmodic dysphonia. He discovered “abnormal patterns of response, increased latencies, and increased amplitudes of recruitment in many tasks including nonphonatory tasks” among all spasmodic dysphonia patients. He also demonstrated abnormal activity in all five intrinsic laryngeal muscles, demonstrating substantially complex and variable dysfunction in the vocal musculature leading to the manifestations of spasmodic dysphonia. This implies that spasmodic dysphonia is a much more heterogeneous disorder than the simple classification of abductor and adductor spasmodic dysphonia suggests. Although evidence as noted above appears promising, the Laryngeal EMG Task Force’s recommendations on laryngeal EMG concludes that further data are needed to assess the reliability of this tool in the diagnosis of spasmodic dysphonia.²¹

The diagnosis of spasmodic dysphonia can be made reliably with the patient’s history and physical examination. Acoustic analysis and laryngeal EMG both have shown promise as aids for difficult cases, but more research is required to better define their role. The cornerstone of diagnosis at this time remains a carefully directed history with appropriate screening questions, speech examination, and flexible laryngoscopy.

■ Treatment

Botulinum Neurotoxin Treatment for Spasmodic Dysphonia

Botulinum neurotoxin type A injections into the intrinsic laryngeal muscles represent the current standard treatment for the treatment of spasmodic dysphonia. There have been over 100 published articles investigating the utility of BoNT injections for spasmodic dysphonia, with the collective evidence overwhelmingly favoring the effectiveness of this modality.

In 1998, Blitzer et al²² reported on their 12-year experience of BoNT treatment for spasmodic dysphonia. They found that 90% of patients improved for 3 to 12 months after injection of BoNT/A, with a need for repeat injections every 3 to 6 months. Two meta-analyses have been performed that considered the efficacy of BoNT, and one blinded, randomized controlled trial has been conducted in which BoNT injection was compared with saline injection and measured with objective acoustic outcomes.^{23–25} BoNT/A markedly reduced perturbation, decreased fundamental frequency range, and improved spectrographic characteristics.

Although the main effect of BoNT is a blockade of the injected muscle at the neuromuscular junction in the peripheral nervous system, this explanation does not seem to correlate with the pathophysiologic model of spasmodic dysphonia or the rather surprising efficacy of this injection, suggesting an effect on the central nervous system. Byrnes

and colleagues²⁶ showed that BoNT injections caused a transient change in the mapping of muscle representation areas in the motor cortex. This has further been suggested by the effect of BoNT on noninjected laryngeal muscles in spasmodic dysphonia.²⁷ In 2007, Antonucci et al²⁸ demonstrated that BoNT is translocated to the afferent synapses in the contralateral hemisphere in mice and rats.²⁸ Although these mechanisms are not completely understood, the efficacy and safety of BoNT have led to its being deemed the primary therapy for spasmodic dysphonia.

The target muscle receiving BoNT injection depends of the relative adductor and abductor features of the spasmodic dysphonia. The standard treatment for adductor spasmodic dysphonia at the majority of voice centers is bilateral EMG-guided transcutaneous injections into the thyroarytenoid muscle, using equal amounts of BoNT; however, there are several variations of this approach. The dose of Botox given, the time course between injections, unilateral versus bilateral injections, and the follow-up can vary between centers and among individual practitioners. In addition, there seems to be great variability in the Botox sensitivity and recovery among patients as well as fluctuations in the disease symptoms. In essence, each patient requires an individualized plan of care, and practitioners may need to alter their injection methods, doses, and schedules accordingly to maximize efficacy.

The efficacy of bilateral thyroarytenoid injections has been the most studied and has the most robust and longest

treatment history. However, some small studies have shown that unilateral injections may have equivalent improvement in voice symptoms and sometimes improved therapeutic profiles.^{29–31} Adams and colleagues²⁹ compared 15 patients receiving a 15-unit (U) unilateral injection of Botox with 11 patients receiving bilateral 2.5-U injections. They found that both the unilateral and bilateral BoNT injections were associated with significant improvements in spasmodic dysphonia, and both types of injections were associated with a significant increase in vocal breathiness at 2 weeks postinjection. However, in using acoustic analysis to compare the two, they found that maximum phonation time, vocal jitter, and the number of voice breaks per second indicated that unilateral BoNT injections may provide superior and longer lasting benefits than bilateral BoNT injections. The same group again compared unilateral and bilateral injections in 1995, treating 25 patients with a 15-U unilateral injection and 25 patients with bilateral 2.5-U injections. They found comparable results at 2 and 6 weeks using acoustic analysis. However, the bilateral group was noted to have a significant reduction in maximum phonation time in comparison with the unilateral group.³⁰ Upile and colleagues³¹ examined 31 patients with adductor spasmodic dysphonia who received either unilateral or bilateral injections. They found that bilateral injections were associated with postinjection voice loss, whereas unilateral injections were not.

Another method for vocal fold injections was described by Ford et al,³² who

used indirect laryngoscopy for guidance in performing thyroarytenoid injections. In their study, a slightly delayed time of onset was noted. However, the efficacy and duration of the injections were not significantly changed from the standard EMG-guided injections. They pointed out that although most otolaryngologists are unfamiliar with laryngeal EMG, most are comfortable with laryngoscopy. Flexible laryngoscopy has been used both to visualize thyroarytenoid injection via a transcutaneous approach and to guide injections through the channel of the laryngoscope.^{33–35} Although convenient, these approaches have limitations. Transoral injection may be limited or made impossible by the patient's gag reflex. Injection through a flexible bronchoscopic needle entails waste of BoNT and makes precision difficult to control.³⁶ The above techniques also do not allow for EMG confirmation of needle placement. We believe that injection with EMG guidance is optimal because it allows for controlled administration of treatment into the more actively contracting regions of the muscle, thus conferring an optimal response.

Injection of the thyroarytenoid muscles may be used for adductor spasmodic dysphonia in patients with previous recurrent laryngeal nerve section, as demonstrated by Blitzer and colleagues.³⁷ This technique was shown to still be effective, although not as effective as in nonsurgical patients. Ludlow and colleagues³⁸ reported a significant reduction in all speech symptoms using bilateral thyroarytenoid injections in the setting of previous recurrent laryngeal nerve section.

In patients with abductor spasmodic dysphonia, the target muscles for denervation are the posterior cricoarytenoid (PCA) muscles. In our practice these injections are generally not performed simultaneously to minimize airway risk. Overinjection of both PCA muscles presents a risk of bilateral paralysis of the primarily abductors of the vocal folds, resulting in airway distress. In other centers, bilateral simultaneous injections may be the norm. Simultaneous injections can be performed safely as demonstrated by Stong and colleagues,³⁹ who performed a series of simultaneous bilateral PCA injections without airway complications.

With the unilateral, staged approach, we recommend reexamination of the larynx at 2 weeks postinjection to determine the therapeutic effect and airway patency. At that time, the contralateral PCA may be injected, usually at half the initial dose. Using this technique, Blitzer et al⁴⁰ noted that patients achieved 70.3% of normal voice.

The interarytenoid muscle was found to be dysfunctional by Hillel and colleagues⁴¹ using five-lead EMG. They found that the interarytenoid muscle can be injected in conjunction with the thyroarytenoid muscle to treat certain cases of refractory spasmodic dysphonia.

Other Treatments

Multiple adjuvant therapies have been employed in the treatment of spasmodic dysphonia. Systemic medications can help reduce symptoms and may work in conjunction with BoNT injections to

prolong the therapeutic effect. The most common medications for the treatment of dystonia are oral anticholinergics. However, the side-effect profiles for these medications are broad and include difficulty with concentration, cognitive impairment, dry mouth, urinary retention, and blurred vision. Local anticholinesterases can ameliorate some of these side effects. Baclofen has been found to have the greatest therapeutic effect with the best side-effect profile.⁷ In the authors' experience, oral anticholinergics are rarely used for patients with isolated voice symptoms related to spasmodic dysphonia.

Surgical management of spasmodic dysphonia remains a controversial area with a storied history. Surgical management of adductor spasmodic dysphonia was first proposed by Herbert Dedo, who initially reported an 85% success rate after unilateral recurrent laryngeal nerve section.⁴ However, subsequent reports and long-term follow-up have shown a higher rate of late failures.⁴² Prolonged or permanent breathiness, unilateral vocal fold paralysis, dyskinesia and synkinesis, as well as recurrence of spasmodic dysphonia spasms have prevented surgery from being a primary modality for treatment. Multiple surgical techniques, including recurrent laryngeal nerve avulsion, laryngeal framework surgery, partial laser thyroarytenoid muscle resection, implantable stimulators, and a denervation-reinnervation technique using the ansa cervicalis, have been used to circumvent this problem with variable success.^{43–47} Although the latter two have shown promise, more data are re-

quired before any judgment of their efficacy can be made.

■ Technique

Our method for laryngeal muscle injection does not require an endoscope or an assistant. We use a 27-gauge insulated needle attached to an EMG, functioning like a monopolar electrode. We use a standard dilution of 4.0 mL of sterile saline/100-U vial of BoNT (Botox; Allergan, Irving, CA), which results in a concentration of 2.5 mouse units per 0.1 mL. This stock solution is then adjusted to deliver a typical volume of 0.1 mL per vocal fold. For instance, to deliver 1.0 mouse unit to the vocal fold, 0.1 mL of stock solution (2.5 U) is diluted to 0.25 mL, creating a concentration of 1.0 U per 0.1 mL. This concentration is meant to prevent large volumes from being injected into the true vocal folds, which could cause airway obstruction. We report below on starting injection doses used at our institution; however, it should be noted that there is significant variation on starting dosages and schedules among practitioners. Chang et al⁴⁸ found that dosage of BoNT/A had a positive correlation with the duration of negative side effects, but a negative correlation with the duration of the normal voice. They posit that their analysis only witnessed the downward trend of what is likely a bell-curve effect in dosing on the normal voice.

Our experience with BoNT injections in the larynx mostly has been with onabotulinum toxin (Botox; Allergan, Inc.),

and therefore most dosing guidelines in this chapter are specific for Botox. Rimabotulinum toxin type B (Myobloc; Solstice Neurosciences, Inc., South San Francisco, CA) and abobotulinum toxin type A (Dysport; Medicis Pharmaceutical, Scottsdale, AZ) are available alternatives, but dosing will need to be adjusted. It should be noted that the diffusion characteristics among the three toxins are slightly different, and that rimabotulinum toxin type B has been associated with a potentially higher autonomic effects (dry mouth).

For patients with suspected blocking antibody formation who respond poorly to BoNT/A, BoNT/B (rimabotulinum toxin type B; Myobloc) has been shown to be a safe and effective alternative.⁴⁹ Blitzer⁵⁰ showed that Myobloc is effective at a dose ratio of roughly 52 U/1 U, and has a more rapid onset of action but a shorter duration.

Adductor Spasmodic Dysphonia

The targeted muscle for treating adductor spasmodic dysphonia is the thyroarytenoid muscle, which arises from the inner surface of the angle of the thyroid cartilage and cricothyroid ligament and inserts on the anterolateral surface of the arytenoid cartilage. The inferomedial fibers of the thyroarytenoid muscle are known as the vocalis muscle (**Fig. 6.1**). The proximity of the thyroarytenoid muscle to the cricothyroid membrane allows for injection of the muscle through the cricothyroid membrane (**Figs. 6.2 and 6.3**). Injection into this muscle is accomplished with a monopolar, hollow, Tef-

lon-coated EMG needle. The patient is placed in a supine position or beach chair position with the neck gently extended. The patient may also be placed in an upright sitting position with the head in neutral position. The thyroid and cricoid cartilages are identified by palpation, delineating the cricothyroid membrane. The needle is bent superiorly 30 to 45 degrees, and then placed through the cricothyroid membrane in or just off of the midline. It is advanced superiorly and laterally. As the surgeon advances the needle, he or she listens for the muscle interference pattern from the EMG. At this point, a characteristic “buzz” on the EMG indicates that the needle is within the laryngeal air column between the two vocal folds, which means that the needle needs to be redirected laterally. Crossing the endolaryngeal mucosa can irritate the patient, triggering a cough reflex. If the needle is redirected slightly lateral to pierce the cricothyroid membrane a few millimeters off the midline, the needle can be directed into the thyroarytenoid muscle without entering the airway, minimizing the irritation. Once the needle is placed in an area that demonstrates crisp motor unit potentials, placement is confirmed with patient vocalization. Asking the patient to say /I/ should augment the EMG response from the thyroarytenoid muscle. With placement confirmed by EMG, the surgeon then aspirates to ensure that the needle has not pierced a blood vessel. BoNT is then injected. Our typical initial treatment dose is a 1- to 1.25-U injection, and a booster can be given in 2 weeks’ time and titrated to the patient’s needs.

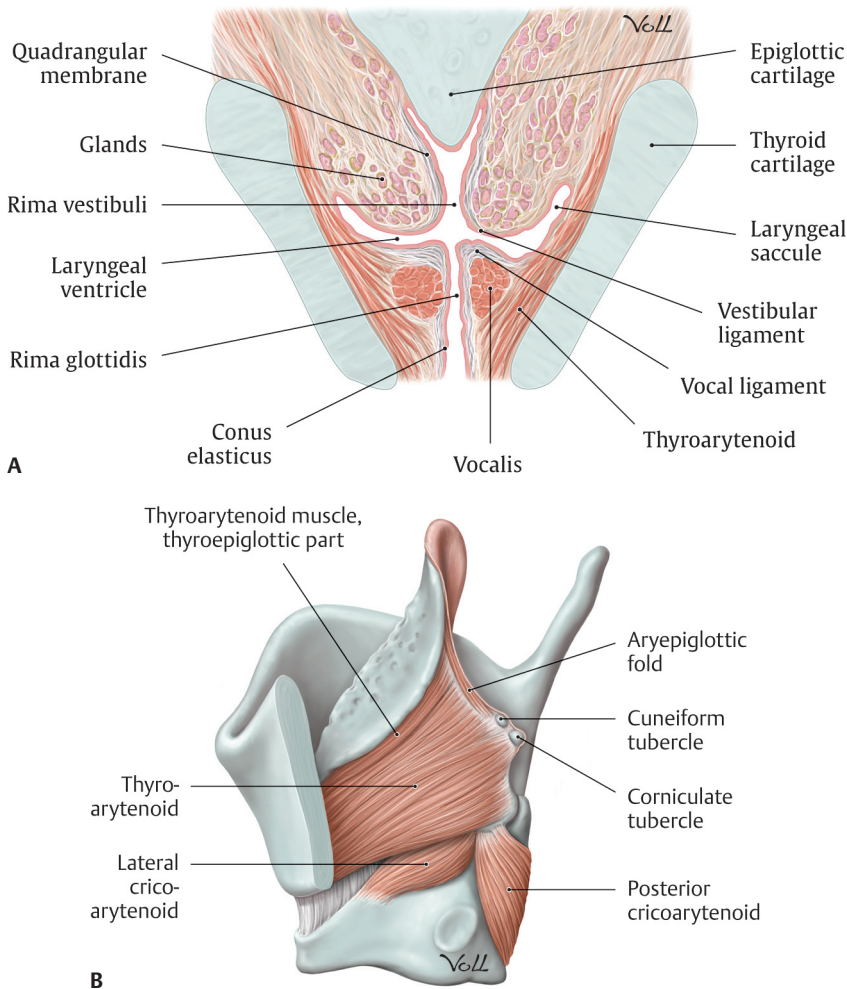


Fig. 6.1 (A,B) Vocal fold anatomy. (From Atlas of Anatomy, © Thieme 2008, Illustration by Markus Voll.)

Abductor Spasmodic Dysphonia

The PCA is the target muscle for treatment in abductor spasmodic dysphonia. It arises from the depressions of the posterior aspect of the cricoid lamina. The muscle runs laterally and superiorly to insert onto the posterior aspect of the ipsilateral muscular process of the arytenoid (**Fig. 6.4**). The position of the posterior cricoarytenoid allows for injection

in one of two ways. The surgeon may rotate the laryngeal framework laterally for direct access to the posterior aspect of the larynx, or the surgeon may pass a needle through the cricothyroid membrane, subglottis, and posterior wall of the cricoid cartilage to reach the muscle.

In the laryngeal rotation technique, the larynx is rotated by the injector to allow access to the posterior face of the cricoid and origin of the PCA. The thumb

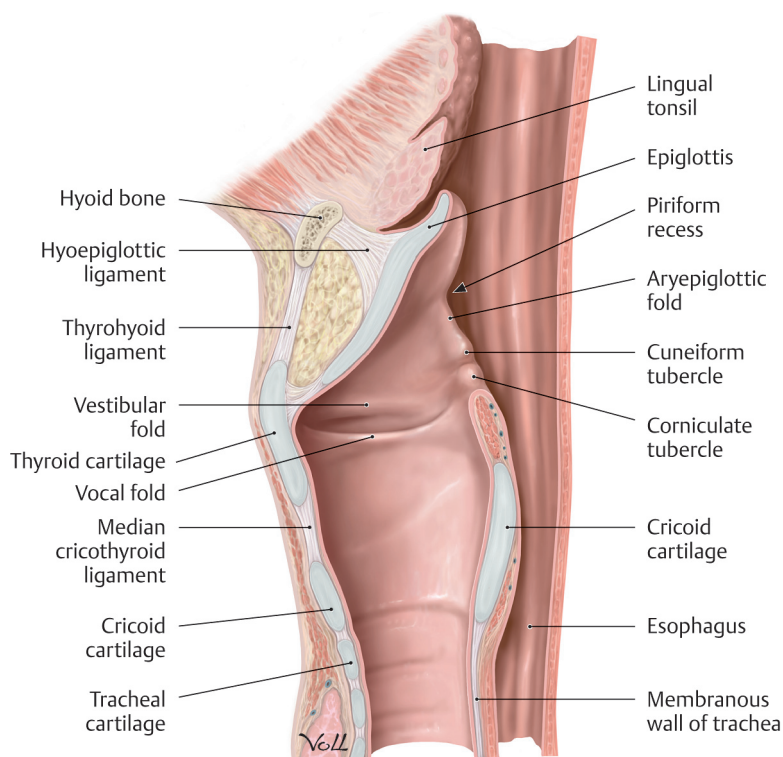


Fig. 6.2 Midsagittal section of larynx. (From Atlas of Anatomy, © Thieme 2008, Illustration by Markus Voll.)

is placed on the posterior aspect of the thyroid cartilage on the side to be injected, with the other four fingers on the contralateral thyroid lamina. The larynx is then rotated to expose its posterior aspect. The needle is then inserted along the lower half of the posterior aspect of the thyroid cartilage and advanced until it abuts the hard surface of the cricoid cartilage (**Fig. 6.5**). It is then pulled back slightly. The patient is asked to sniff to confirm the position of the needle on EMG. This method works best on patients with a thin neck and high, mobile larynx. The patient should be positioned comfortably with the neck and shoulders relaxed to allow for minimal muscle activity.

The transglottic method involves traversing the airway and boring through the cricoid cartilage. The needle is inserted through the cricothyroid membrane in the midline, guided across the subglottic air space, and through the posterior lamina of the cricoid cartilage on one side of the midline or the other (**Fig. 6.6**). Generally, with this approach, an intratracheal injection of plain lidocaine is helpful in preventing the patient from coughing. This does not hinder EMG signaling as the target muscle is on the opposite side of the cricoid cartilage from the injection. Placement is again confirmed by having the patient sniff. This technique is more difficult in older patients, in whom the cartilage is

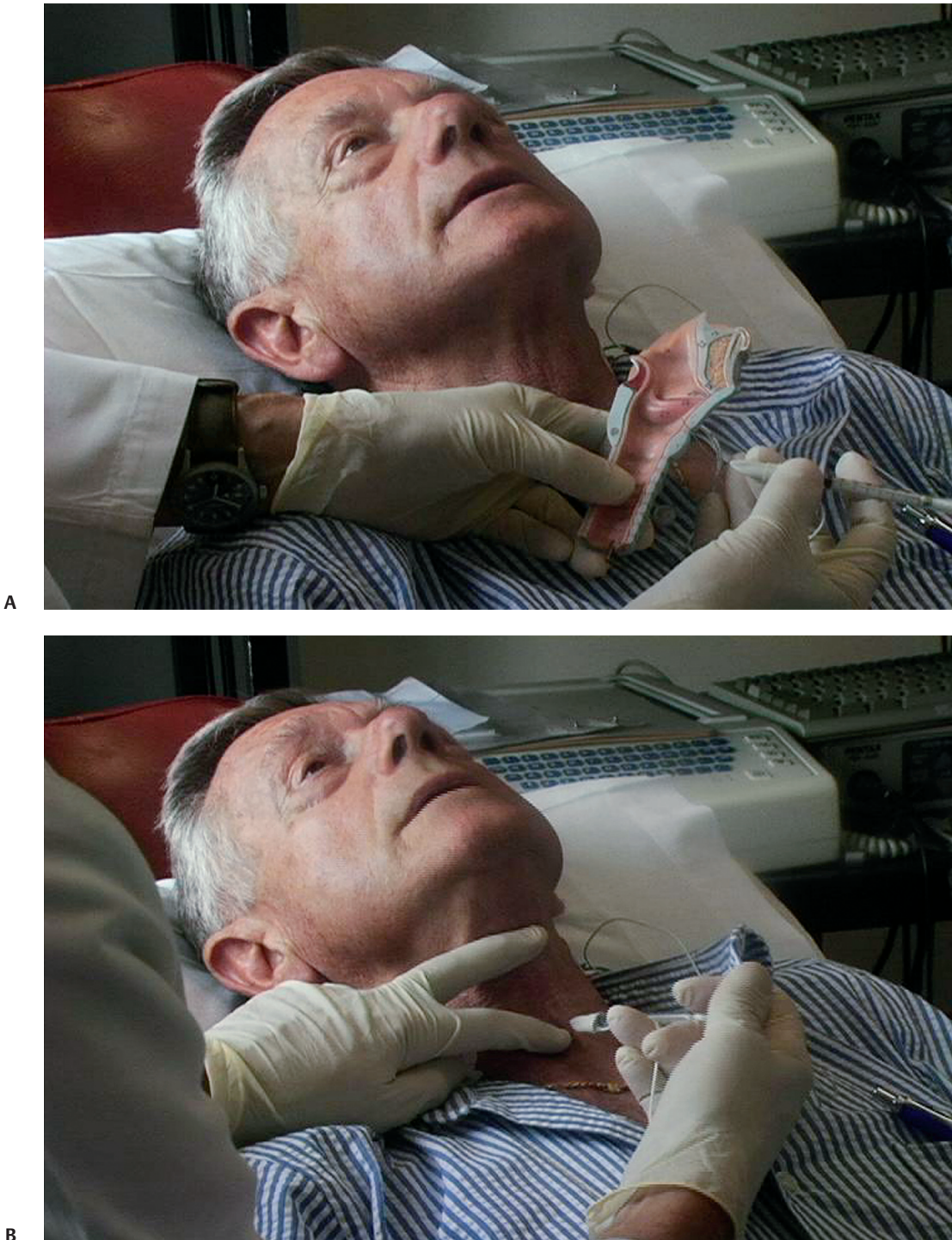


Fig. 6.3 (A,B) Transcricothyroid thyroarytenoid injection technique.

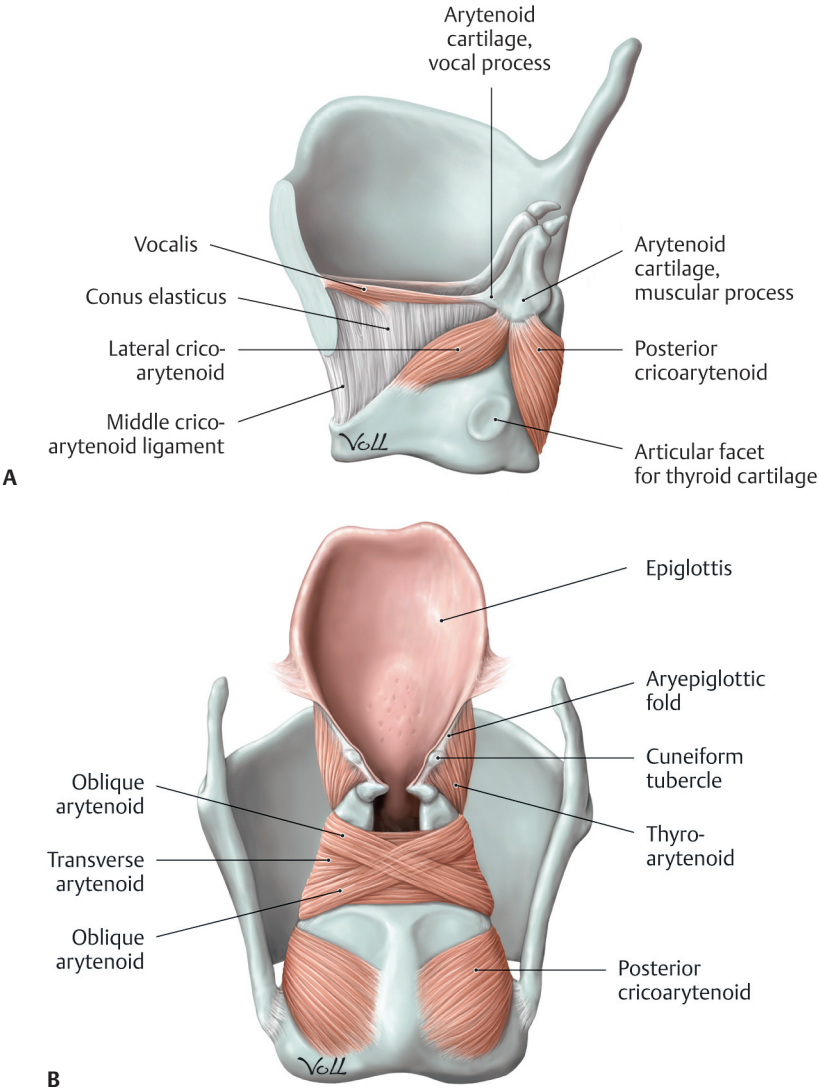


Fig. 6.4 (A,B) Posterior cricoarytenoid muscle. (From Atlas of Anatomy, © Thieme 2008, Illustration by Markus Voll.)

increasingly calcified. We begin injection with a dose of 3.75 U or 0.15 mL of BoNT to one PCA muscle. The effect this has on the injected muscle is used for dose adjustment 2 weeks later, at the time of injection of the contralateral PCA. In their original investigation of this technique, Blitzer et al⁴⁰ found that 19% of patients improved after unilateral injection, and patients on average experi-

enced an overall improvement to 70% of normal function.

Refractory Spasmodic Dysphonia

Some patients do not have a good response to BoNT injections. In these cases other etiologies of dysphonia should be evaluated. This appears to be more prevalent in abductor spasmodic dysphonia,

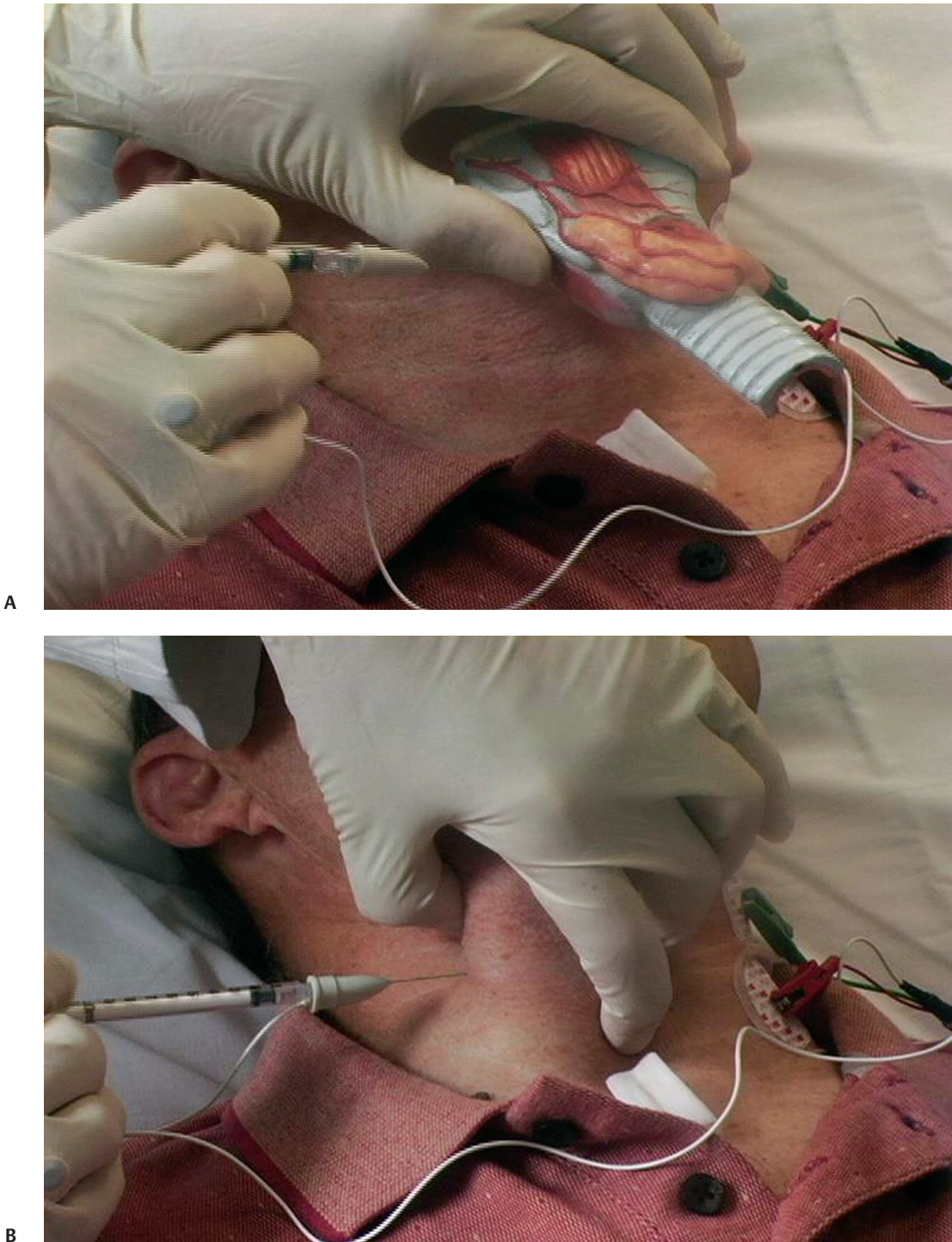


Fig. 6.5 (A,B) Laryngeal rotation posterior cricoarytenoid (PCA) injection technique.

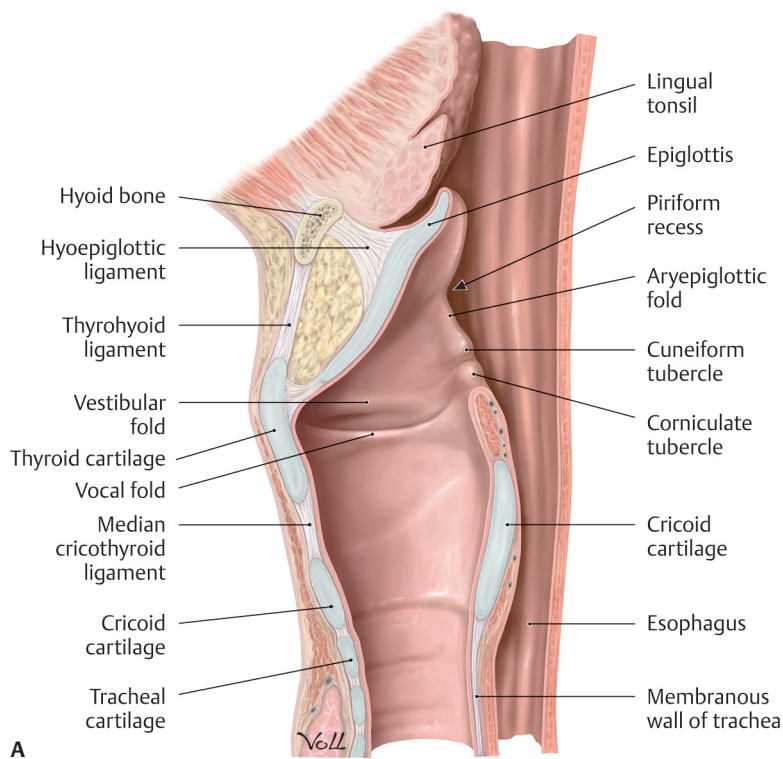


Fig. 6.6 (A) Transglottic PCA muscle. (From Atlas of Anatomy, © Thieme 2008, Illustration by Markus Voll.) **(B)** Transglottic PCA injection technique.

and is likely due to the fact that the weakness required to break the abductor spasms brings on unacceptable airway symptoms. Unfortunately, other patients develop refractory dysphonic spasms despite a good initial result with toxin injections. Klotz et al⁵¹ demonstrated that multiple different muscles can be involved in refractory spasmodic dysphonia and EMG may be used to show which muscles are involved in a particular case, allowing for better targeting of toxin injections.

Another approach is a trial injection of additional muscle groups. Interarytenoid muscle injection may be performed in patients with adductor spasmodic dysphonia in whom traditional thyroarytenoid injections have not provided relief. Hillel⁸ in 2001 initially noted prominent EMG abnormalities of the interarytenoid muscle in patients with adductor spasmodic dysphonia. Hillel et

al⁴¹ then studied the effect of interarytenoid BoNT injections in 23 patients. They found a good response in 10 patients, five of whom had been refractory to traditional BoNT injection. The interarytenoid muscle is the only unpaired intrinsic muscle of the larynx. It is comprised of the transverse and oblique portions (**Fig. 6.7**). The transverse portion arises from the posterior surface of both arytenoid cartilages, crossing from one to the other. The oblique portion originates on the posterior aspect of the muscular process, crosses the midline, and inserts on the apex of the contralateral arytenoid cartilage. Some fibers continue as the aryepiglottic muscle.⁵² The interarytenoid muscle may be approached transglottically, piercing the muscle between the arytenoid towers.²² It may also be approached through the cricothyroid membrane using laryngeal EMG for guidance.⁵³ Other potential muscles that

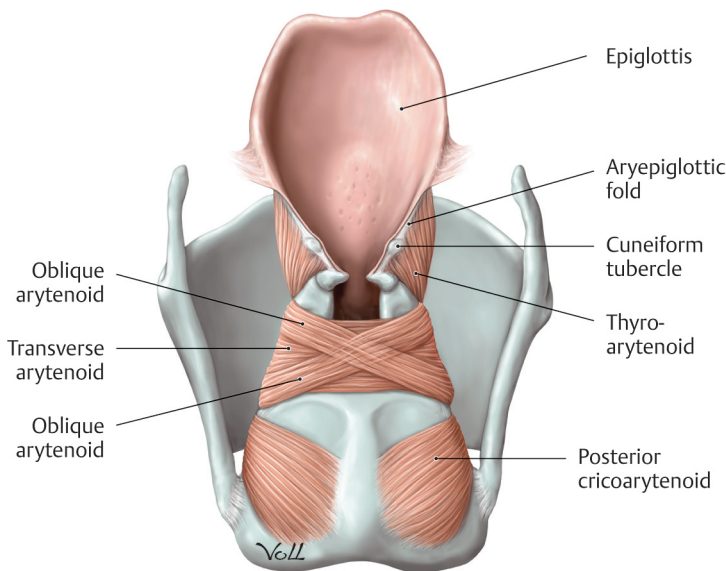


Fig. 6.7 Interarytenoid muscles. (From Atlas of Anatomy, © Thieme 2008, Illustration by Markus Voll.)

have been successfully targeted are the supraglottic musculature in the aryepiglottic fold or the false vocal fold. If patients seem to transition from breathy phonation directly back to hyperfunctional phonation, alternating each vocal fold with larger doses but at shorter intervals may be successful. Finally, if patients seem to lose all response to one serotype of toxin, a different serotype may lead to a good result.

Cricothyroid muscle injections have been used, based on research performed by Ludlow and associates,⁵⁴ showing abnormal cricothyroid activity in these patients. The cricothyroid muscles are bilateral broad muscles that arise off the lateral aspects of the anterior cricoid and go lateral and superior toward the lateral thyroid lamina (**Fig. 6.8**). The needle is inserted along the lateral boundary of the cricothyroid space and is directed superiorly and laterally, staying superficial to the thyroid lamina. When the needle encounters insertional motor activity, the patient is instructed to speak a high-pitched /I/ or perform a pitch glide from the lower register into fal-

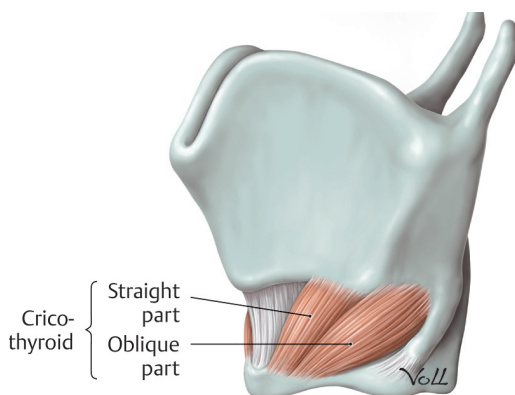


Fig. 6.8 Cricothyroid muscle. (From Atlas of Anatomy, © Thieme 2008, Illustration by Markus Voll.)

setto. The confirmation is an EMG signal that escalates with higher pitch. The typical starting dose is 3.75 U per side.

■ Follow-Up

Patients are monitored clinically to assess their dose response. There is a high degree of variability in the dose-response rate and the duration of effect among patients with spasmodic dysphonia. In addition, patient preference and convenience must be taken into account. Patients who cannot attend follow-up with great regularity may require a higher dose of BoNT even though it entails temporary breathiness, whereas patients with easy access to the clinic may prefer short-duration, smaller doses resulting in virtually no breathiness. As noted in the Chang et al⁴⁸ study, there is likely a threshold dose after which increased doses increase side effects without providing significant benefit. Bilateral or unilateral minidoses of 0.1 to 0.5 U every 6 to 8 weeks may avoid the breathy period altogether. Some patients with adductor spasmodic dysphonia may also respond better to staggered unilateral doses. Efficacy of treatment with this pathology is determined by meeting the patient's goals of care as much as possible. Holden et al⁵⁵ retrospectively reviewed a series of 13 adductor spasmodic dysphonia patients, and found that they were able to reach their optimal dose after an average of 2.2 injections. They also found that the patients who started with a dose of 1.5 U to each thyroarytenoid had a more stable dose than those who started at a dose of 2.5 U to

each thyroarytenoid. Lastly, they noted the interval between injections remained constant once the optimal dose was achieved. This correlates with the findings of Brashear and associates,⁵⁸ who noted consistent time intervals between BoNT injections in the treatment of cervical dystonia. An alternative treatment is using Botulinum toxin B, especially in patients who may have become secondary non-responders due to development of an antibody to the toxin.^{56,57}

■ Complications and Pitfalls

Treatment with BoNT results in an initial period of marked muscle weakness lasting several days, followed by a months-long plateau of somewhat milder weakening that constitutes the therapeutic effect. This is likely because of the two-stage mechanism of neural recovery from BoNT, in which partially cleaved SNAP-25 is rapid early in the treatment, but completely cleaved SNAP-25 requires 3 months for full repair or replacement.⁵⁹ SNAP-25 (synaptosomal-associated protein-25) is involved in transcytosis of the neurotransmitter acetylcholine across the cell membrane into the neuromuscular junction. The result of this initial period after thyroarytenoid injection is breathiness. Occasionally, clinically insignificant aspiration may be noted. After posterior cricoarytenoid injection, the initial period may be marked by dyspnea. Injection of the posterior cricoarytenoid muscles could result in airway narrowing and a sensation of tightness.

The need for caution in injecting posterior cricoarytenoid muscles likely ex-

plains the decreased satisfaction rate with treatment of abductor spasmodic dysphonia. However, Stong et al³⁹ have shown that bilateral, simultaneous posterior cricoarytenoid injections are safe, and Klein et al⁶⁰ have demonstrated that bilateral posterior cricoarytenoid muscle injections may improve results and patient satisfaction.

As complete neural recovery is achieved, patients revert back to their initial symptomatology. Patients are required to cycle through the process of disease symptoms, symptoms of acute weakness, a treatment window, and then disease symptoms again. Each patient will have a slightly different response to the treatment, and will have different voice requirements. For patients who rely on their voice professionally, a regimen of smaller injections with a decreased window of breathiness may be beneficial. Patients who live far from their treatment centers may wish to maximize their dose to lengthen the time between treatments. Thus, patients' treatment regimens must be individually tailored.

■ Conclusion

Spasmodic dysphonia is a focal laryngeal dystonia of central nervous system origin. Surgical treatment options have been either disappointing or insufficiently studied. The treatment of choice currently is BoNT injections into selected laryngeal muscles. Proper injection technique and carefully tailored dosing schedules provide patients with a safe and effective treatment.



Video 4 Abductor Spasmodic Dysphonia (Laryngeal Dystonia)

This patient has breathy breaks on connected speech segments accompanied by facial twitching. His abductor breaks require treatment of the posterior cricoarytenoid muscle(s). First, a small amount of xylocaine is placed via the membrane into the subglottis. His injection is given via the cricothyroid membrane with a hollow-bore Teflon-coated EMG needle. The needle is placed through the membrane, through the air passage, and through the rostrum of the cricoid cartilage until the PCA muscle is impaled; whereupon a burst of electrical activity is seen on EMG. The PCA is then injected with 3.75 U/0.15 cc. Both PCAs are not done simultaneously, so as to avoid stridor or an airway emergency.



Video 5 Abductor Spasmodic Dysphonia

In these two patients, the laryngeal complex is rotated, and the EMG needle is passed posterior to the posterior lamina and through the inferior constrictor muscle. It impales the PCA muscle over the back side of the cricoid rostrum. The patients are asked to “sniff,” thereby activating the muscle, and 3.75 U/0.15 cc of Botox is injected.



Video 6 Adductor Spasmodic Dysphonia

A hollow-bore Teflon-coated EMG needle is used via the cricothyroid membrane to inject the thyroarytenoid muscle complex. Once the muscle is engaged, the patient is asked to phonate and electrical activity is seen on the EMG. On average, 1.0 U/0.1 cc in each muscle.



Video 7 Adductor Spasmodic Dysphonia

Another example of the transcricothyroid membrane approach to injecting the TA muscle complex with EMG guidance. An average of 1.0 U/0.1 cc is given bilaterally.

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Cervical Dystonia

Tanya K. Meyer, Joel Guss, and Ronda E. Alexander

Cervical dystonia (CD) is the most common focal dystonia.¹ It results in the sustained contraction of the cervical musculature, leading to abnormal posturing of the neck, head, and shoulder. The injection of botulinum neurotoxin (BoNT) into the overactive muscles of CD patients can effectively treat the abnormal neck movements and pain caused by this disorder. The abnormal movements of the neck and head can result in twisting (torticollis), tilting (laterocollis), flexion (anterocollis), or extension (retrocollis). Additional movements are shoulder elevation and lateral movement of the head/neck with relation to the chest wall.

■ Epidemiology

The incidence of CD is 9 to 30 per 100,000 people in the United States, and the prevalence may vary among ethnic groups.^{1,2} Studies have shown a higher incidence among women, with an ap-

proximate 2:1 female-to-male ratio.³ In greater than 70% of cases, the disease begins between the fourth and sixth decades of life, with a peak incidence in the fifth decade.⁴ A family history of dystonia is seen in 12%. Progression of dystonia to other anatomic areas is seen in up to one third of cases.³

Symptoms typically worsen over the course of the first 5 years before stabilizing. Spontaneous remission is seen in 10 to 20% of individuals lasting days to years, although these are temporary and most patients eventually relapse.^{3,5} Employment status is significantly affected by CD, with over 30% requiring reduced work hours or reduced responsibilities and 19% resulting in loss of employment.⁶

■ Pathophysiology

As in all dystonia, the pathophysiology of idiopathic CD is not well understood, although it is generally thought to be an

Table 7.1 Typical Muscles Involved in Cervical Dystonia

<i>Movement</i>	<i>Muscles Involved</i>
Rotational torticollis	• Ipsilateral splenius capitis • Contralateral sternocleidomastoid
Laterocollis	• Ipsilateral sternocleidomastoid • Ipsilateral splenius capitis • Ipsilateral scalene complex • Ipsilateral levator scapulae • Ipsilateral trapezius
Shoulder elevation	• Ipsilateral levator scapulae • Ipsilateral trapezius
Retrocollis	• Bilateral splenius capitis* • Bilateral upper trapezius*
Anterocollis	• Bilateral sternocleidomastoid* • Bilateral scalene complex* • Bilateral submental complex*

* For bilateral injections, decrease the individual dose 50 to 60% to avoid unwanted dysphagia, in the anterior injections, or neck weakness and difficulty holding the head straight, in the posterior injections.

(Adapted from Brashear A, The botulinum toxins in the treatment of cervical dystonia. *Semin Neurol*, 2001;21(1) 85–90; Benecke R, Dressler D. Botulinum toxin treatment of axial and cervical dystonia. *Disabil Rehabil* 2007;29:1769–1777; and Deuschl G, Heinen F, Kleedorfer B, Wagner M, Lucking CH, Poewe W, Clinical and polymyographic investigation of spasmodic torticollis. *J Neurol*. 1992 Jan. 239(1) 9–15.)

abnormality in central motor processing. There is a genetic component to the development of dystonia, but trauma and drug exposure can also be a precedent to focal dystonia.⁷ Currently, the main theories are decreased central inhibition, sensory deficit with sensorimotor mismatch, aberrant neuroplasticity, and abnormal basal ganglia discharge.^{8–13} Although any muscle in the neck may be involved, **Table 7.1** lists the common muscles with the associated head/neck movements. There may be multiple muscles involved with co-contraction of agonist and antagonist muscles.

■ **Clinical Manifestation**

Idiopathic CD usually begins with abnormal head/neck movements before pro-

gressing to other areas. Head tremor and neck spasms are cardinal features of CD, and the majority of affected patients complain of pain.

Approximately half of patients are able to identify a sensory trick, or *geste antagonistique*, to help control their abnormal neck spasms.¹⁴ Typically this trick constitutes placing the hand on the side of the face or neck, and this contact reduces the muscle spasm without actually mechanically opposing the spasm. Some patients can even imagine the sensory trick to diminish symptomatic spasms.¹⁵ The pathophysiology of the sensory trick is unknown. Although early in the course of disease these tricks are helpful in most patients, they tend to lose effectiveness as the disease progresses.

Additional palliative factors include relaxation, alcoholic beverages, and “morn-

Table 7.2 Differential Diagnosis of Torticollis

- Cervical spine fracture or disease
- Peritonsillar or retropharyngeal abscess
- Drug reaction (tardive dystonia)
 - Neuroleptics: droperidol, haloperidol, pimozide, Thorazine, Compazine
 - Dopamine receptor antagonists: metoclopramide
- Wilson's disease
- Klippel-Feil syndrome
- Sandifer syndrome
- Bobble-head doll syndrome (with third ventricle cyst)
- Progressive supranuclear palsy
- Posterior fossa tumor
- Spinal cord tumor or syrinx
- Multiple sclerosis
- Systemic lupus erythematosus
- Huntington's disease
- Psychogenic dystonia

ing benefit,” in which symptoms are less intense just after waking. CD is exacerbated by activity, stress, and fatigue.

On physical examination, muscles should be palpated for hypertrophy, activity, and contracture/fibrosis, although it may be difficult to differentiate among these conditions. Areas of pain should be noted. By convention, the direction of the rotation is defined by the chin, so right-turning torticollis means that the chin deviates to the patient's right. Abnormal head and neck postures can occur in multiple planes. Rotational torticollis occurs around the longitudinal axis, laterocollis rotates the head in the coronal plane tilting the ear to the shoulder, and anterocollis and retrocollis rotate the head in the sagittal plane; additionally, there may be sagittal or lateral deviation of the base of neck from the midline. Deviations in only one plane are seen in less than one third of patients.⁵

It is important to remember that an abnormal head and neck posture with cervical musculature spasm can be a

manifestation of other disease processes, both acute and chronic. Thus, a full history and diagnostic workup should be performed. Wilson's disease should be excluded in all patients under 50 through evaluation of serum ceruloplasmin and slit lamp examination. Lesions and abnormalities of the brain, posterior fossa, and spinal cord can be excluded through imaging studies. A full neurologic examination should be performed. The presence of fasciculations, cerebellar signs, cranial nerve weakness, or cortical dysfunction should alert the clinician that there may be additional pathology present (**Table 7.2**).

■ Management

Medical Therapy

Although the efficacy of oral drug therapy is limited, there are medications that can ameliorate the severity of, or serve as adjuncts in the treatment of, CD (**Table 7.3**).

Table 7.3 Medications Used for Dystonia

Name	Mechanism	Beneficial Effects	Adverse Effects
Trihexyphenidyl Ethopropazine Benztropine	Anticholinergic	• In a double-blind placebo-controlled trial using trihexyphenidyl, 71% had a clinically significant response, with 42% maintaining long-term benefit.³³ • In a prospective, randomized, double-blind controlled trial, botulinum neurotoxin type A (BoNT/A) was shown to be more effective in treatment of abnormal movements and pain as compared with trihexyphenidyl.³⁴ Anticholinergics are considered the most beneficial oral pharmacologic agent.³⁵	• Dry mouth, blurred vision, imbalance, forgetfulness, fatigue, depression, micturition disturbance • Can use pyridostigmine to overcome peripheral effects³⁶ • Can use pilocarpine eyedrops for blurred vision³⁶ • Dose usually limited by side effects • Need to discontinue slowly to prevent rare occurrence of neuroleptic malignant syndrome
Benzodiazepines	GABA agonist	• Muscle relaxation	• Sedation
Baclofen	GABA-B agonist	• Muscle relaxation, works at spinal cord level	• Sedation
Tetrabenazine	Presynaptic catecholamine depleting agent	• A review of over 500 patients treated over 15 years showed marked improvement in 63% of patients with idiopathic dystonia.³⁷	• Akathisia, depression, sedation, fatigue, insomnia, anxiety, parkinsonism

GABA, γ -aminobutyric acid.

Surgery

Denervation and myotomy techniques to address the abnormally functioning musculature have been explored for centuries. Isaac Minnius sectioned the sternocleidomastoid muscle to address CD in 1641. Campbell de Morgan in London sectioned the spinal accessory nerve in 1866. William Halsted, Harvey Cushing, John Finney, Theodor Kocher, Fritz De Quervain, and Guillaume Depuytren are among the reported names of esteemed

surgeons who have attempted surgical amelioration of torticollis.¹⁶ Although cervical rhizotomy was the standard technique prior to the introduction of BoNT therapy, it has been largely abandoned due to limited efficacy in the face of a relatively high burden of side effects. In general, it is thought that surgical denervation is an option for patients refractory to BoNT injections.^{17,18}

Brain lesioning has been used since the early 1940s for treatment of CD, with variable results. Targets include se-

lected regions of the basal ganglia and thalamus. These procedures can cause significant side effects including weakness, dysphagia, and dysarthria in 6 to 47% of patients.¹⁹ These destructive techniques have been supplanted by deep brain stimulation (DBS) due to the more favorable risk profile and promising results.²⁰

Deep brain stimulation is used to treat several types of movement disorders (chronic pain, Parkinson's, depression, dystonia, tremor, Tourette's) and has the advantage over brain lesioning of being reversible and adjustable. There are reported neuropsychiatric side effects, including mood disorders and hypersexual behavior, but these can theoretically be modulated by adjustment of the stimulation.²¹ Permanent cognitive complications are rare. Studies have shown excellent therapeutic efficacy and safety for DBS in patients with disabling CD.²⁰

Chemodenervation

The introduction of chemodenervation with BoNT of the cervical musculature has dramatically improved the prognosis and quality of life of patients with cervical dystonia. Off-label treatment of patients with CD with BoNT/A started in the late 1980s and due to an excellent effect was quickly accepted and widely used. Since 2000, the use of BoNT/A and BoNT/B has been a Food and Drug Administration (FDA)-approved indication for CD and has become the favored treatment for this condition.

Botulinum neurotoxin can cause weakness in the injected muscles, leading to

atrophy and ameliorating the spasmodic contractions. The injections can alleviate the abnormal head postures, tremor and pain for approximately 3 to 4 months. This therapy has been proved effective in many double-blind placebo-controlled and open trails with fewer side effects than other pharmacologic therapies or surgical procedures prior to the advent of DBS.^{22,23}

There are dosing differences between the different serotype of BoNT and also different brands of the same serotype. Although a set conversion formula has not been established, studies have recommended an approximate ratio of Botox/Dysport/Myobloc of 1 unit (U) Botox/3 to 5 U Dysport/ 40 to 50 U Myobloc.^{22–24} Although there is variability in the number of muscles injected, the number of injections per muscle, and the dose of BoNT used, the average dose for CD is 200 U of Botox or 500 U of Dysport.²³

Direct efficacy comparisons among brands and serotypes have been reported. A double-blind, randomized study comparing BoNT/A (Botox) and BoNT/B (Myobloc) included 139 CD patients and evaluated efficacy, adverse events, and duration of effect. In this study, peak efficacy, as measured by a standard scale, did not differ between the two preparations. The duration of benefit was approximately 2 weeks shorter with Myobloc, and adverse events such as dysphagia and dry mouth were more frequent with Myobloc, although still mild.²⁵

Overall, approximately 20% of patients treated at least one time choose not to continue chronic injections because of

an unsatisfactory response, the lack of effect, or the high cost of treatment.²⁶ Additionally, 15 to 30% of patients are cited as primary nonresponders (never benefit from injections); the nonresponse is thought to be due to muscle contractures, inadequate dosing, inaccurate muscle selection, or inaccessible dystonic musculature. Anterocollis is particularly nonresponsive to injections because of involvement of the inaccessible deep anterior prevertebral musculature. Secondary treatment failures (loss of efficacy following previous successful injections) are thought to occur in 10 to 15% of patients, and up to one third of patients are found to have anti-

bodies to BoNT by the mouse neutralization assay.^{14,27}

■ Injection Technique

Successful treatment of patients depends on knowledge of neck anatomy and accurate assessment of involved musculature. The sternocleidomastoid, trapezius, splenius capitis, and levator scapulae are most commonly injected (**Figs. 7.1, 7.2, 7.3, 7.4, and 7.5**). Comella et al²⁸ reported a significantly greater magnitude of improvement in patients whose injections were administered under electromyographic guidance than in those

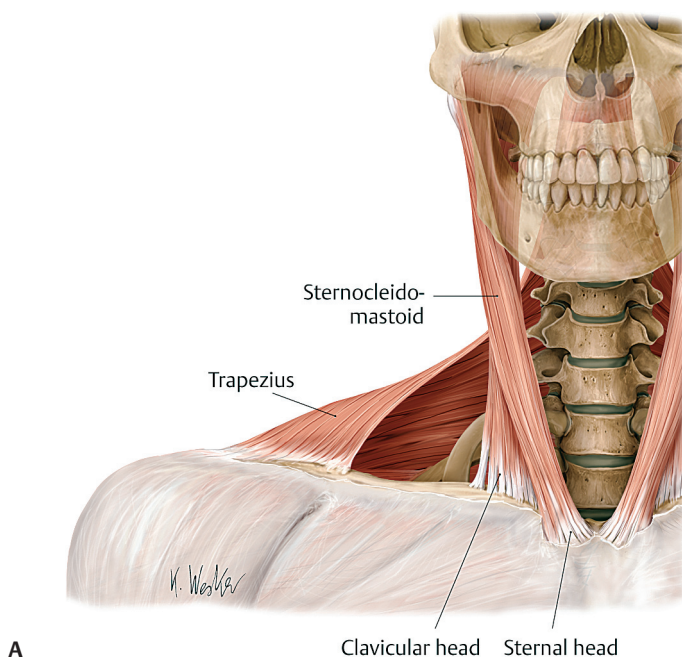


Fig. 7.1 (A) Sternocleidomastoid, trapezius, and levator scapulae muscles. (From *Atlas of Anatomy*, © Thieme 2008, Illustration by Karl Wesker.)

in whom only anatomic localization and clinical examination was used.²⁸ Yet the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology still concludes that the use of electromyography remains controversial.²⁹

Rotational head turning is the simplest symptom to treat and usually involves injection of the contralateral sternocleidomastoid and the ipsilateral splenius capitis and semispinalis capitis. These

patients may also have pain, which may give some indication as to the appropriate location of the injection.³⁰ It is important to use the lowest dose possible and to maximize the time between injections, to minimize side effects and also minimize antigenic load. For the sternocleidomastoid, the injections are given in the rostral third of the muscle, which helps limit dysphagia. Injections of the posterior neck musculature can cause some neck weakness (such as lifting the chin

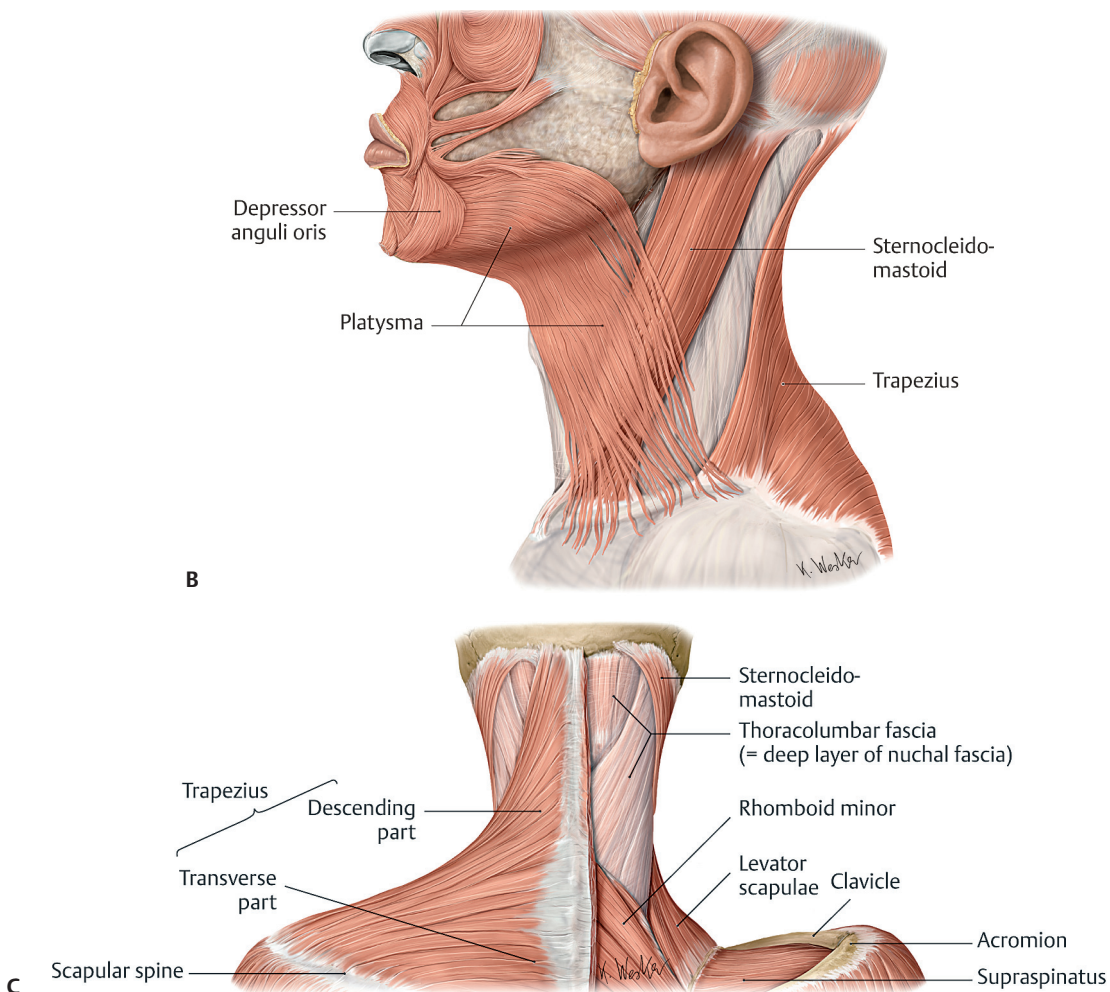


Fig. 7.1 (B, C) (Continued)

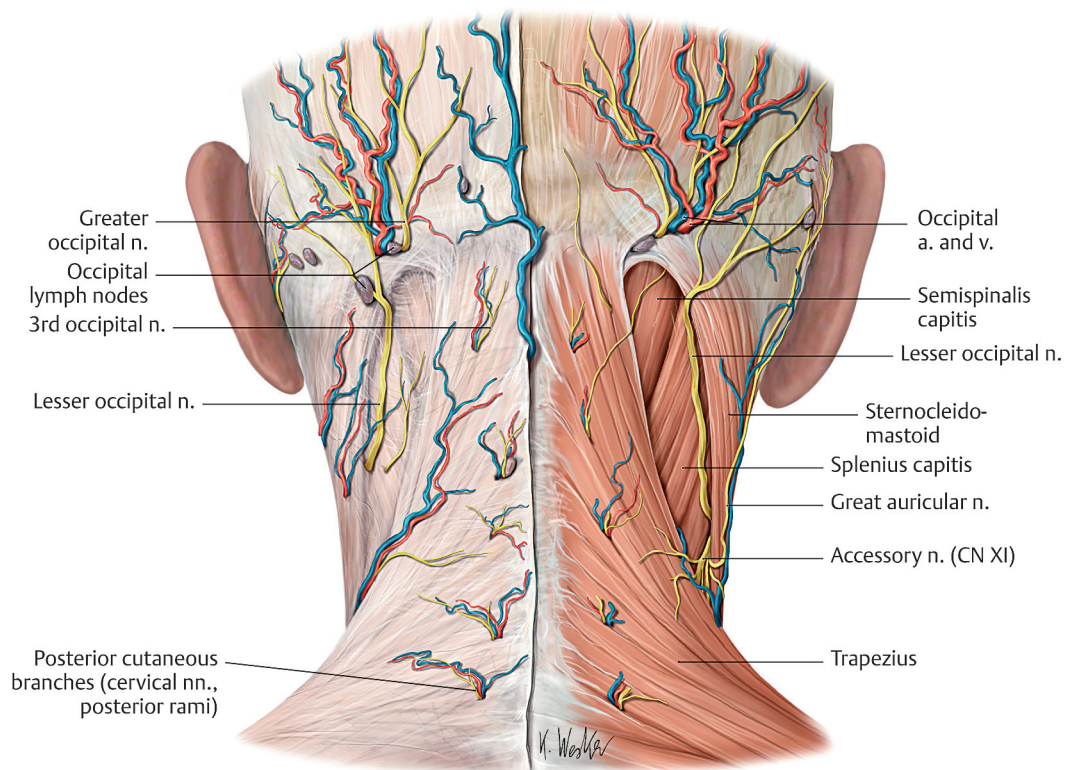


Fig. 7.2 Splenius capitis muscle. (From Atlas of Anatomy, © Thieme 2008, Illustration by Karl Wesker.)



Fig. 7.3 Sternocleidomastoid muscle injection.



Fig. 7.4 Splenius capitis muscle injection.

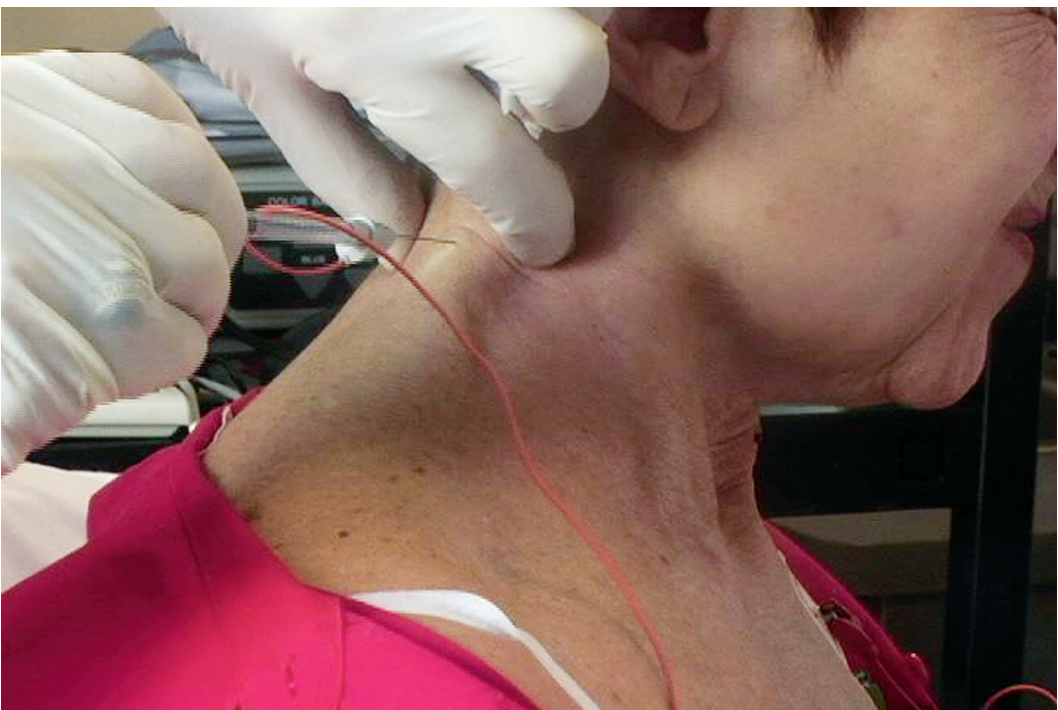


Fig. 7.5 Trapezius muscle injection.

off of the chest) and rarely difficulty opening the jaw if the injections track anteriorly toward the pterygoid musculature.

Ipsilateral laterocollis (head tilt) is usually caused by involvement of the ipsilateral splenius capitis, levator scapulae, and sternocleidomastoid. Injections of the levator scapulae have rarely been associated with brachial plexus injury or pneumothorax.³¹ Retrocollis and head tremor can be treated with splenius capitis and semispinalis capitis injections. Anterocollis is the most difficult movement to treat and involves injection of the scalene complex and of the anterior deep paravertebral musculature, which is difficult to access transcutaneously.

■ Conclusion

Cervical dystonia is the most common form of focal dystonia and affects more than 90,000 people in the United States. It is important to perform a full neurologic evaluation to exclude other causes of abnormal neck movement in new cases. CD causes significant patient disability and loss of quality of life. BoNT chemodenervation is the most common treatment for these patients and can alleviate the abnormal neck postures, relieve pain, and prevent the muscle fibrosis and cervical spine degenerative complications associated with the constant abnormal muscle spasms.³²



Video 8 Cervical Dystonia (Torticollis)

This patient has lateral collis with a head tilt and rotation to the right. She receives EMG-guided injections of 5 U/0.1 cc in multiple sites of the following muscles: sternocleidomastoid, splenius capitis, platysma, trapezius, and occipitalis.

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■ S E C T I O N I I ■

Other Motor Disorders

Hemifacial Spasm and Facial Synkinesis

*Lesley French Childs, Daniel Novakovic,
and Scott R. Gibbs*

■ Hemifacial Spasm

Hemifacial spasm is a disorder of recurrent, involuntary twitches of facial muscles that are peripherally induced. A disorder that typically begins in middle age and more commonly in women, hemifacial spasm often first involves the orbicularis oculi and spreads slowly to other facial muscles. There is a progression seen from increased blinking initially to forced closure of the eyelids. Later, twitching of the lower face can develop. The most common spasms include eye closure and mouth retraction/elevation. The longer the duration of the disorder, the more likely it is for patients to develop midfacial weakness as well. Although it is benign, this disorder affects patients both cosmetically and functionally. Unfortunately, the disorder is chronic,

with only rare reports of spontaneous recovery. Defazio et al¹ describes two patients in a series of 65 patients who experienced complete and long-lasting symptom relief during their second or third year of treatment with botulinum neurotoxin (BoNT). In a Cochrane review, only one randomized placebo-controlled trial involving 11 people was identified; it this was performed by Yoshimura et al in 1992. Indeed, BoNT treatment was noted to be superior to treatment with a placebo. This, in combination with numerous other case series, suggests that BoNT is effective and safe for treating hemifacial spasm. The paucity of placebo-controlled trials comparing the efficacy of BoNT with placebo is likely due to the significant success of treatment with the toxin reported in open studies. Researchers likely would find it ethically

difficult to randomize patients to simply examine efficacy. However, further trials to evaluate the technique of injection, dose, immunogenicity, and long-term efficacy would provide value.²

The etiology is thought to be due to vascular compression of the facial nerve by an aberrant vascular loop, specifically the posterior inferior cerebellar artery (PICA). Other causes of compression include tumors or vascular malformations. After vascular pressure has been exerted on the facial nerve, a secondary demyelination is thought to ensue. In an article investigating unusual causes of hemifacial spasm, specifically those other than vascular compression at the root exit zone of the facial nerve, Han et al³ emphasizes radiologic investigations for achieving accurate diagnoses. Specifically, cases of tumor compression, vascular malformation, and dolichoectatic vertebrobasilar arteries are discussed.

Treatment for hemifacial spasm includes oral doses of antiepileptic drugs (such as carbamazepine and baclofen as well as benzodiazepines), neurosurgical decompression of the seventh cranial nerve, or intramuscular BoNT injections. The BoNT injections avoid the need for oral medications, with their associated side effects and limited efficacy, as well as the risks associated with a major intracranial operation.⁴ In the neurosurgical literature, Kong and Park⁵ report that in numerous reported series, deafness occurred in 1.6 to 2.6% of cases and permanent facial weakness occurred in 3.4 to 4.8% of those undergoing microvascular decompression. Because of the potential complications and the possibility

of recurrence of spasms, most patients and physicians prefer using BoNT for long-term management of hemifacial spasm. In fact, much evidence supports the use of BoNT as the first-line treatment for hemifacial spasm.⁶

Recently, Rudzińska et al⁷ noted that the often-associated sensory and autonomic complaints of hemifacial spasm also responded to treatment with BoNT. Specifically, tearing, eye irritation, and a “clicking” sound (attributed to contractions of the stapedius muscle) were reduced after treatment with the toxin. This finding is likely due to the interference of transmission at the cholinergic synapses of the parasympathetic and postganglionic sympathetic nervous system.⁷

■ Facial Synkinesis

One of the most troubling sequelae of facial nerve paralysis is synkinesis, which is the presence of unintentional motion in one area of the face produced during intentional movement in another area of the face. Synkinetic movements can be socially debilitating and can also be quite painful, with simultaneous spasm of multiple muscle groups. The most common form of synkinesis is oculo-oral, involving involuntary oral commissure movement with voluntary eye closure.

The etiology of synkinesis is thought to be multifactorial, with evidence supporting the role of aberrant axonal regeneration as well as central involvement in the form of facial nucleus hyperexcitability. Bajaj-Luthra et al⁸ quantitatively analyzed the patterns of synkinetic fa-

cial movements on both the affected and unaffected sides. Patients with oculororal synkinesis were noted to have increased modiolar motion during eye closure relative to controls. (The modiolus is where several facial muscles converge toward a focus, just lateral to the buccal angle, to form a fibromuscular mass with three-dimensional mobility.) More specifically, in patients with synkinesis, the modiolar motion was noted to be asymmetric and increased in the horizontal and vertical planes. In consideration of both the affected and unaffected sides of the face, Neely et al⁹ have described two types of synkinesis: synergistic synkinesis, in which movement on the affected side is similar to what might be seen on the unaffected side, but in excess thereof; and paradoxical synkinesis, in which the secondary facial movement is in a direction considered antagonistic to normal facial movement.

One of the earliest reported physiotherapy programs with consistent positive results for synkinesis rehabilitation is mime therapy, a technique developed in the Netherlands by collaboration between clinicians and mime actors.¹⁰

The most common therapeutic modalities for the treatment of facial synkinesis include facial neuromuscular retraining and BoNT administration, which can augment the retraining.

■ Workup

Hemifacial spasm needs to be distinguished from a focal dystonia (which is

thought to be of central origin), as well as from blepharospasm (which is mostly bilateral), myokymia of the orbicularis oculi (which usually does not involve the lower face or cause complete eyelid closure), and synkinesis after Bell's palsy. Thus, a thorough neurologic, ophthalmologic, and head and neck examination is crucial to accurately diagnose hemifacial spasm.

In patients with atypical features such as facial weakness, facial numbness, a decreased corneal reflex, or any other cranial nerve abnormalities, a space-occupying lesion should be excluded with magnetic resonance imaging/angiography. If such a lesion is identified, neurosurgical consultation may provide benefit.

■ Anatomy

The patient sits comfortably upright or is placed in a reclining position. If lower facial injections are to be administered, electromyography (EMG) guidance is typically employed, and ground and reference electrodes are placed over the sternocleidomastoid muscle (SCM). The location of the desired injections should be marked on the skin, which is cleansed with an alcohol swab. Injections are administered using a 30- or 32-gauge needle or a hollow 27-gauge, Teflon-coated, monopolar electromyography injection needle on a 1-mL tuberculin syringe. The orbicularis oculi injections are administered in the same manner as those for the treatment of blepharospasm (see Chapter 2). Treatment of the lower face

is delayed until a response is achieved from the orbicularis oculi injections. In many cases, a periorbital injection to decrease the passive blink and the eye closure will also stop the mouth twitching and elevation. Usually a reassessment at 2 weeks is needed before injecting the lower face.

The dose for the injections is typically 2.5 units (U)/0.1 cc of Botox in the pretarsal orbicularis oculi muscle (**Fig. 8.1**) and in the medial and lateral upper eye-

lid (**Figs. 8.2 and 8.3**), 2.5 U in the orbicularis oculi 1 cm from the lateral canthus (**Fig. 8.4**), and 2.5 U in the lateral position of the inferior orbicularis oculi of the lower lid (**Fig. 8.5**). The dose can be decreased for more mild symptoms. Patients with concurrent medial brow spasm may achieve further benefit from treatment of the procerus and corrugator supercilii muscles.

The procerus muscle is a pyramidal slip arising from the nasal bone and upper

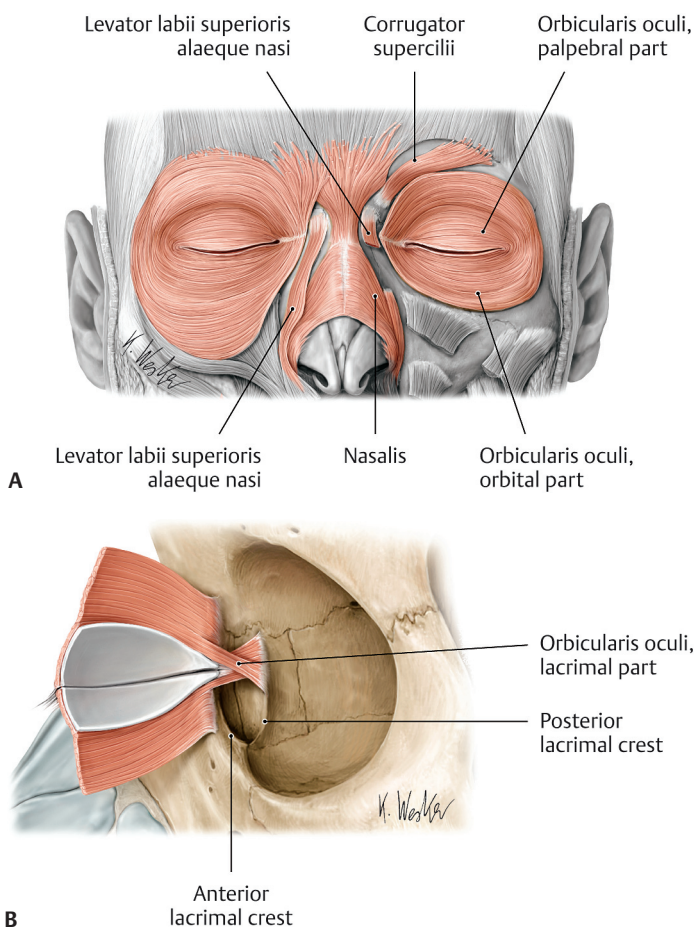


Fig. 8.1 (A,B) Orbital anatomy. (From THIEME Atlas of Anatomy: Head and Neuroanatomy, © Thieme 2007, Illustration by Karl Wesker; and from Atlas of Anatomy, © Thieme 2008, Illustration by Karl Wesker.)



Fig. 8.2 Medial pretarsal orbicularis muscle injection.

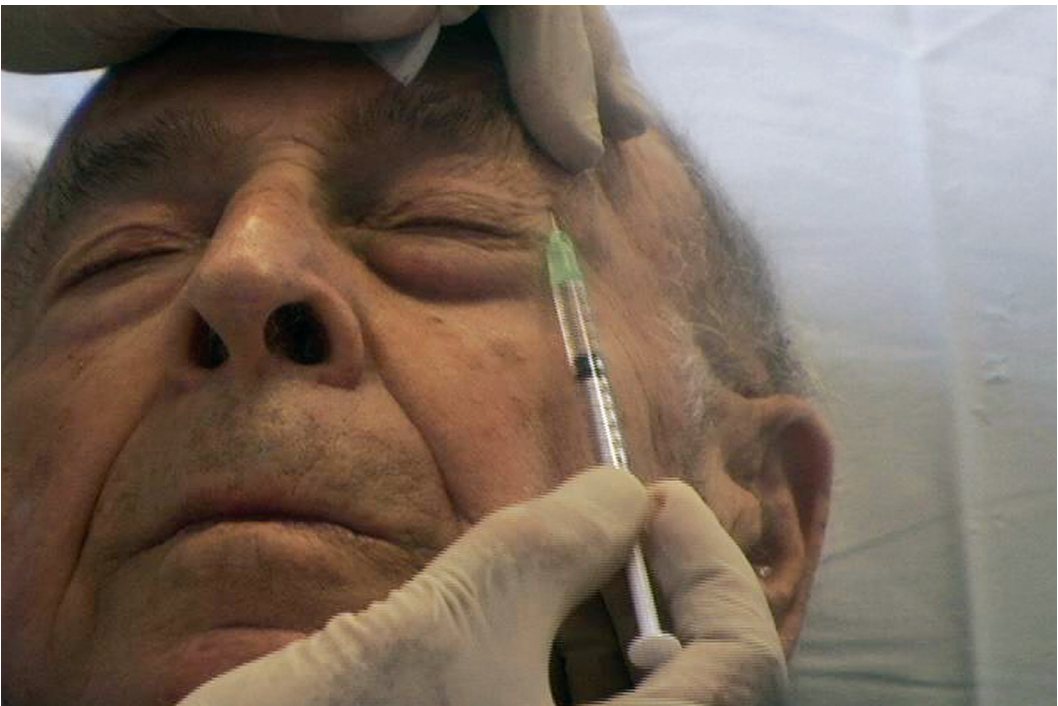


Fig. 8.3 Lateral pretarsal orbicularis muscle injection.



Fig. 8.4 Injection lateral to the lateral canthus.

lateral cartilage that inserts into the skin between the eyebrows. Its purpose is to draw down the medial angle of the eyebrows, producing transverse rhytids over the bridge of the nose. The corrugator supercillii arises from the medial end of the superciliary arch. Its fibers pass between the palpebral and orbital portions of the orbicularis oculi and insert into the deep surface of the skin, above the central orbital arch. The corrugator draws the eyebrow downward and medialward, producing vertical rhytids (**Fig. 8.5**).¹¹

For treatment of the lower face, 1.25 to 2.5 U can be injected under electromyographic control into the zygomaticus major, zygomaticus minor, levator anguli oris, depressor anguli oris, risorius, and platysma (**Fig. 8.5**).

A brief review of these lower facial muscles is appropriate at this point, as a thorough understanding of facial anatomy is crucial for proper treatment technique. The zygomaticus major muscle arises from the zygomatic bone in front of the zygomaticotemporal suture. The muscle descends obliquely and inserts into the angle of the mouth. This muscle draws the angle of the mouth backward and upward, as in laughing. The zygomaticus minor originates from the malar bone and inserts into the outer portion of the upper lip. It draws the upper lip backward, upward, and outward.

The levator anguli oris arises from the canine fossa, just below the infraorbital foramen. These fibers insert into the angle of the mouth. The depressor anguli oris arises from the oblique line of

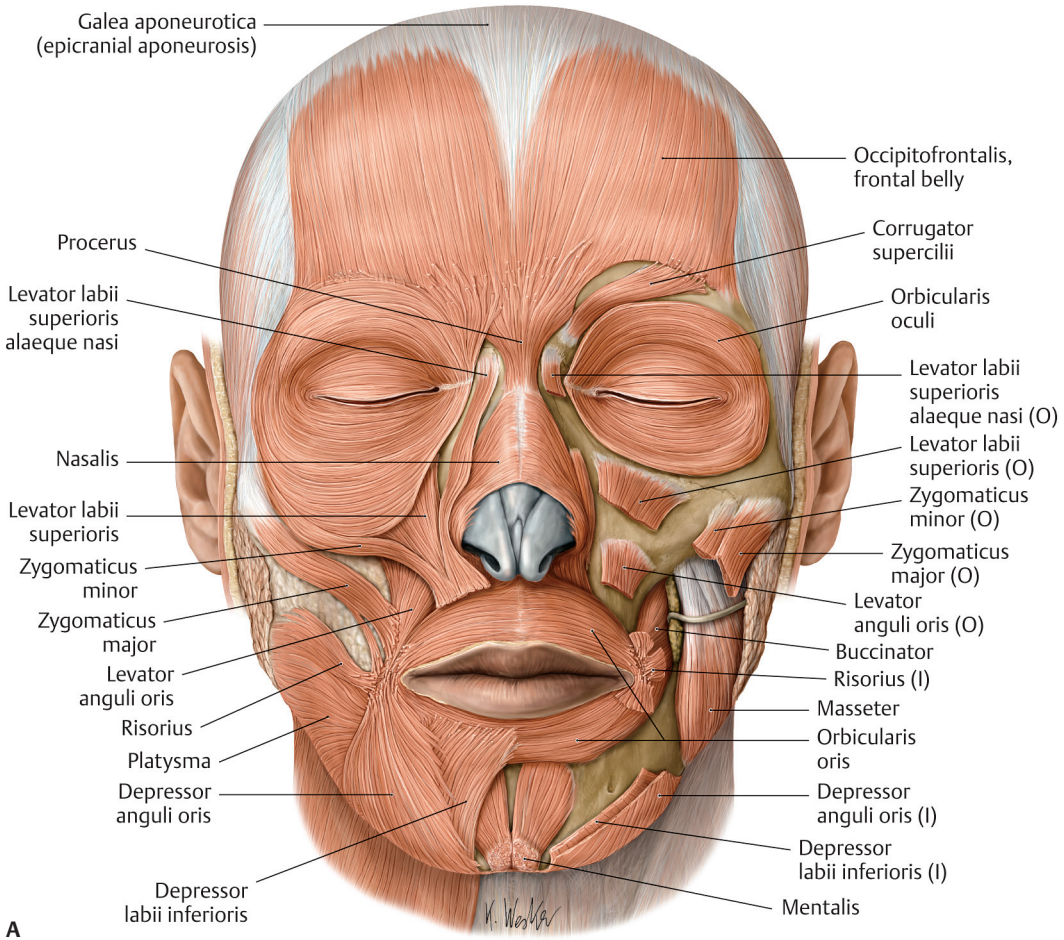


Fig. 8.5 (A) Muscles of facial expression. (From Atlas of Anatomy, © Thieme 2008, Illustration by Karl Wesker.) (continued on next page)

the mandible and inserts into the angle of the mouth. The action of this muscle depresses the angle of the mouth, acting antagonistically to the action of the levator.

The risorius arises in the fascia over the masseter and passes horizontally forward, superficial to the platysma. It then inserts into the skin at the angle of the mouth. Its action retracts the angle of the mouth.

The platysma is a broad sheet arising from the fascia covering the upper parts

of the pectoralis major and deltoid. The fibers cross the clavicle and proceed obliquely upward and medially along the side of the neck. The anterior fibers interlace, below and behind the symphysis menti, with the fibers of the muscle of the opposite side; the posterior fibers cross the mandible, some being inserted into the bone below the oblique line, others into the skin and subcutaneous tissue of the lower part of the face, many of these fibers blending with the muscles about the angle and lower part

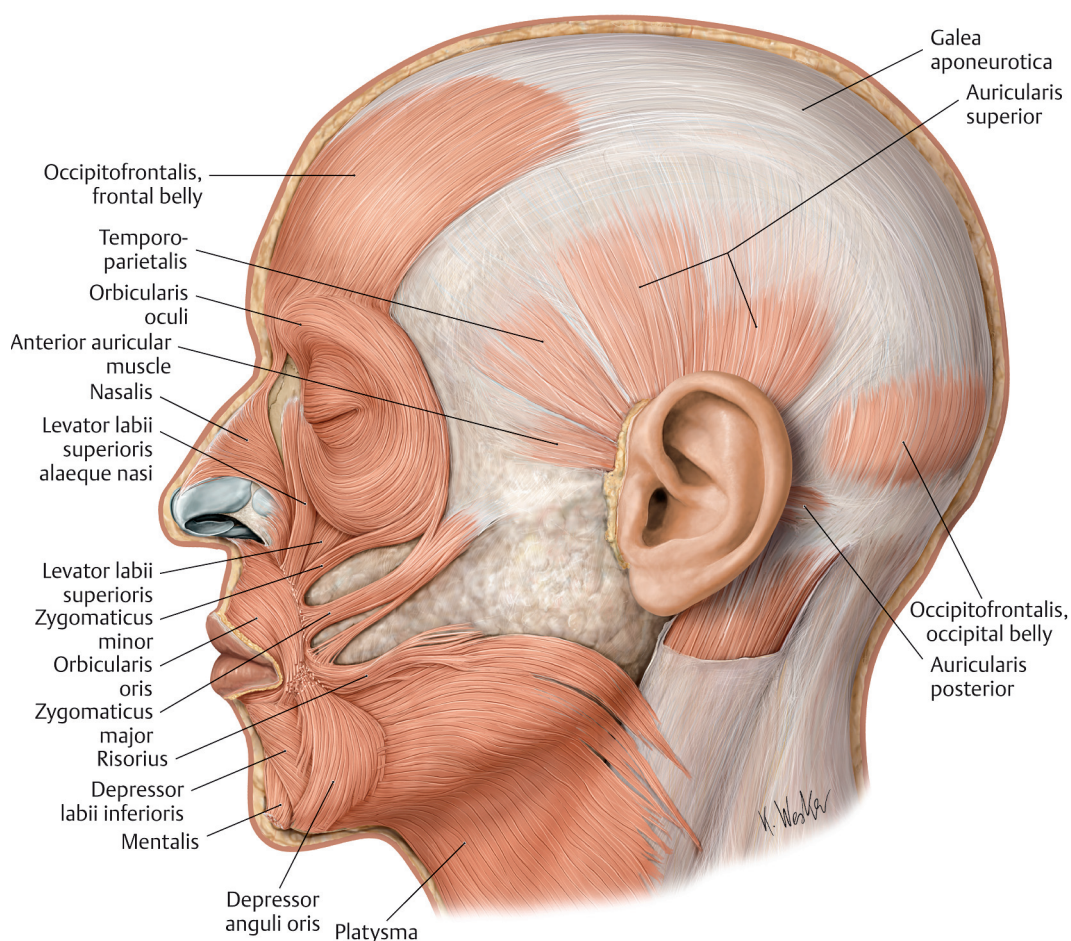


Fig. 8.5 (B) (Continued)

of the mouth. The platysma retracts and depresses the angle of the mouth.¹¹

The doses used to treat synkinesis are typically lower than those used to treat hemifacial spasm, as the facial musculature is weaker at baseline. The goal is to weaken the abnormally stimulated muscles to allow for more symmetrical movement and postures at rest. The upper and lower face is done at the same initial setting. Optimal dosing is decided on an individuated basis based on the patient's active and passive facial symmetry. The zygomaticus muscles, levator anguli oris, depressor anguli oris, ri-

sorius, and platysma are the most often injected muscles under EMG control.⁴

■ Follow-Up

Patients should return at 2 to 3 weeks for evaluation of the orbital effects and persistence of facial spasms. If additional injections of the orbicularis oculi are necessary, further treatment can be administered at the follow-up visit. More commonly (to minimize side effects and adequately gauge response) additional treatment is deferred to the subsequent

3-month injection visit, when a higher total dose is utilized.⁴

■ Complications and Pitfalls

Complications include upper lid ptosis from diffusion of the toxin into the levator muscle. It is possible to help stimulate the muscle with a sympathomimetic eyedrop such as apraclonidine 0.5 or 1.0% drops (1 drop t.i.d.). Exposure keratitis may result from a decreased blink, requiring artificial tear solution or a patch over the eye temporarily.

The nasolabial line may flatten from injections of the toxin, which may lead to an asymmetric smile, which may be

corrected by smaller doses on future visits or injecting the normal side to lessen the disparity. Additionally, contour variations may be remedied by the injection of fillers.⁴

■ Conclusion

The successful treatment of hemifacial spasm and facial synkinesis affords an improved quality of life for patients, on both a physical and emotional level. BoNT injections have proven to be a safe and effective treatment for these disorders and represent a preferable alternative to the other medical and surgical therapies currently available.



Video 9 Hemifacial Spasm

Excessive function, such as repetitive tight eye closure, produces irritability and left hemifacial twitching. The most hyperfunctional areas of the patient's orbicularis oculi muscle are injected subcutaneously with 2.5 U/0.1 cc of Botox. For many patients, treating the eye and reducing spasms also quiets the mid-face. If not, the zygomaticus and levator labi superioris may also have to be treated.



Video 10 Facial Synkinesis

This patient has a post-Bell's palsy left facial synkinesis. Notice her mid-face elevation on the left with eye closure. Her left orbicularis oculi muscle is injected in several places subcutaneously with 2.5 U/0.1 cc at each of the marked points.

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Hyperfunctional Facial Lines

Brian E. Benson and Andrew Blitzer

Facial aging is a multifactorial process involving changes to skin, subcutaneous fat, muscle, and the underlying facial skeleton. Notable among these changes are hyperfunctional facial lines, rhytides, which develop with repetitive muscle activity. Over time, these lines deepen and remain apparent, even when the underlying musculature is relaxed. Both photodamage and smoking significantly accelerate these changes.

The ability of botulinum neurotoxin (BoNT) to reduce the appearance of facial lines was first noted in patients receiving treatment for hyperfunctional disorders such as hemifacial spasm and blepharospasm. Subsequent placebo-controlled studies confirmed the safety and efficacy of botulinum neurotoxin type A (BoNT/A) for the reduction of dynamic upper facial lines.^{1,2} BoNT/A (Botox Cosmetic; Allergan, Irving, CA) was approved by the Food and Drug Administration (FDA) in 2002 for the temporary treatment of moderate to severe

glabellar lines, and this remains the only FDA-approved cosmetic indication for both onabotulinumtoxinA (Botox) and abobotulinumtoxinA (Dysport; Medicis Pharmaceutical, Scottsdale, AZ). Data from the American Society for Aesthetic Plastic Surgery 2010 database indicates that treatment with BoNT/A for the reduction of facial lines is currently the most common aesthetic procedure in the United States, and its use has increased 50% during the 8-year survey period from 2002 to 2010. In 2010, 2.4 million procedures were performed with BoNT/A and 1.3 million procedures were performed with hyaluronic acid fillers, which together accounted for approximately 65% of all nonsurgical cosmetic procedures performed that year.³

There is now a substantial body of evidence supporting the safety and efficacy of BoNT/A for reduction of dynamic upper facial lines. However, extensive clinical experience has shown both BoNT/A and BoNT/B to be highly efficacious primary

or adjunctive treatments of not just glabellar rhytides, but also rhytides associated with hyperfunctional frontalis, orbicularis oculi, nasalis, orbicularis oris, depressor anguli oris, mentalis, and platysma muscles. It is also effective at reducing brow ptosis and the appearance of a hypertrophic pretarsal orbicularis oculi muscle.⁴⁻⁷ In addition to the reduction of dynamic facial lines, recent research suggests that mild glabellar lines *in repose* are also reduced, although the mechanism of this “smoothing” phenomenon is not completely understood.⁸

Reduction of dynamic facial lines may result in a more youthful appearance, as well as decreased inaccurate social interpretation of facial gestures suggesting anger or frustration. The goal of BoNT/A treatment is not only to reduce the appearance of rhytides, but also to prevent the development of deep rhytides and thereby delay or avoid more invasive rejuvenation procedures. Based on an expanded facial rejuvenation paradigm incorporating three-dimensional volume restoration, BoNT/A is frequently used in conjunction with dermal fillers to meld facial movement control, recontouring, and volume enhancement to provide a more relaxed, youthful appearance.⁴

■ Workup

Patients should be interviewed regarding their medical history, medications, and prior cosmetic or reconstructive surgery. BoNT injection is contraindicated in patients with infection at the injection

site, in patients with a known hypersensitivity to any ingredient in the formulation (including human albumin, saline, milk [abobotulinumtoxinA only]), in those receiving aminoglycosides, and in pregnant or lactating women. BoNT injection is relatively contraindicated in patients with disorders of the neuromuscular junction, myasthenia gravis, motor neuron disease, or Eaton-Lambert syndrome.⁹ Furthermore, caution should be exercised in those patients with surgical alteration of facial anatomy, excessive dermatochalasis, and deep dermal scarring, as the effect of BoNT/A may be limited regarding the desired cosmetic outcome. Patients with active viral or bacterial illness have higher levels of circulating antibodies, which may decrease the efficacy of BoNT/A. Therefore, we recommend against BoNT/A injections in the setting of infection.

■ Botulinum Neurotoxin Formulations

Both BoNT/A (Botox, Dysport) and BoNT/B (Myobloc [rimabotulinumtoxinB]; Solstice Neurosciences, Inc., South San Francisco, CA) are approved for cosmetic use. InconobotulinumtoxinA (Xeomin; Merz Pharmaceuticals, Greensboro, NC) is not approved for cosmetic use. Although Botox/Dysport conversion ratios of 1:2.5, 1:3, and 1:4 have been reported in the literature, it is important to note that potency units for BoNT products are specific to each preparation, and are not interchangeable.⁴ BoNT/B is generally considered less suitable for cosmetic use

due to pain at the injection site due to low pH and shorter duration of effect.^{4,10} Compared with Botox, Dysport may have a larger diffusion radius.¹¹

General Considerations

Treatment planning and goals must be individualized according to specific anatomic variables including the location and depth of rhytids, size and position of facial musculature, brow position, eye shape, and skin type, as well as individual characteristic facial gestures and ethnic background. Examination during muscle activation as well as during repose is required to appreciate the contributions of the various muscles to facial rhytides. It should be noted that substantial differences exist between various ethnic aesthetic ideals. Therefore, additional treatment planning and customization may be required with different ethnic groups. Clarifying goals, addressing anxieties, and dispelling misconceptions regarding the effects of BoNT/A are particularly important components of every consultation.

Most practitioners counsel the patient regarding the previously mentioned factors, as well as the role of dermal fillers in facial volume contouring, so that realistic goals and expectations may be established prior to initiating treatment with BoNT/A alone or in conjunction with other nonsurgical procedures. Although this chapter does not discuss volume contouring, the clinician is encouraged to become familiar with its use.

Doses are basic guidelines that should be modified based on individual anatomy,

patient preference, and clinician judgment. For BoNT/A, the solution is reconstituted according the standard formulation of 4 mL of saline per bottle, yielding 2.5 units (U) per 0.1 cc. These injections are typically performed using a 1.0-cc tuberculin syringe. An alternative reconstitution strategy is to use 1 mL of saline per 100-U bottle, yielding 1 U per 0.01 cc, injected with a 0.1-cc syringe. This technique creates smaller injection aliquots, which decreases the appearance of the bolus at the injection sites. The choice of the injection needle and syringe depends on the individual technique as well as on the specific application. Most practitioners use 29- to 32-gauge, ½- to 1¼-inch needles with 1-cc tuberculin syringes, 0.3-cc syringes, or 0.1-cc syringes (BD Medical, Franklin Lakes, NJ). The 0.1-cc syringes are particularly suited for use with the 1 U/0.01 cc dilution. Smaller gauge needles decrease injection pain, but become dull sooner, with subsequent loss of this advantage after multiple injections.

Although topical anesthesia is generally not required, some practitioners may use topical anesthetic such as lidocaine, ice, or massagers such as the Buzzy (MMJ Laboratories, 32 Sutherland Place NE, Atlanta, GA 30307) for vibration anesthesia in sensitive areas.

The depth of injection depends on the thickness of the skin, the amount of subcutaneous adipose tissue, and the size of the injected muscle. Most cosmetic injections do not require electromyographic (EMG) guidance, but it may be helpful in locating deeper or thinner muscles, such as the risorius or platysma.⁹

Although there are no evidence-based guidelines, most practitioners massage the injection site after injection to produce hydrostatic pressure to facilitate some diffusion, but they instruct their patients to avoid manipulating these areas. Although contraction of the treated muscles has been shown to increase neurotoxin uptake, heavy physical exertion immediately after the injection is discouraged.

Complications of cosmetic BoNT/A injection can be grouped into three categories: local, locoregional, and systemic. Local complications include pain, erythema, ecchymosis, and hematoma formation. Locoregional complications are related to excessive weakening of facial and neck musculature or diffusion of the BoNT/A to adjacent muscles, resulting in brow ptosis, eyelid ptosis, facial asymmetry, oral incompetence, dysarthria, and

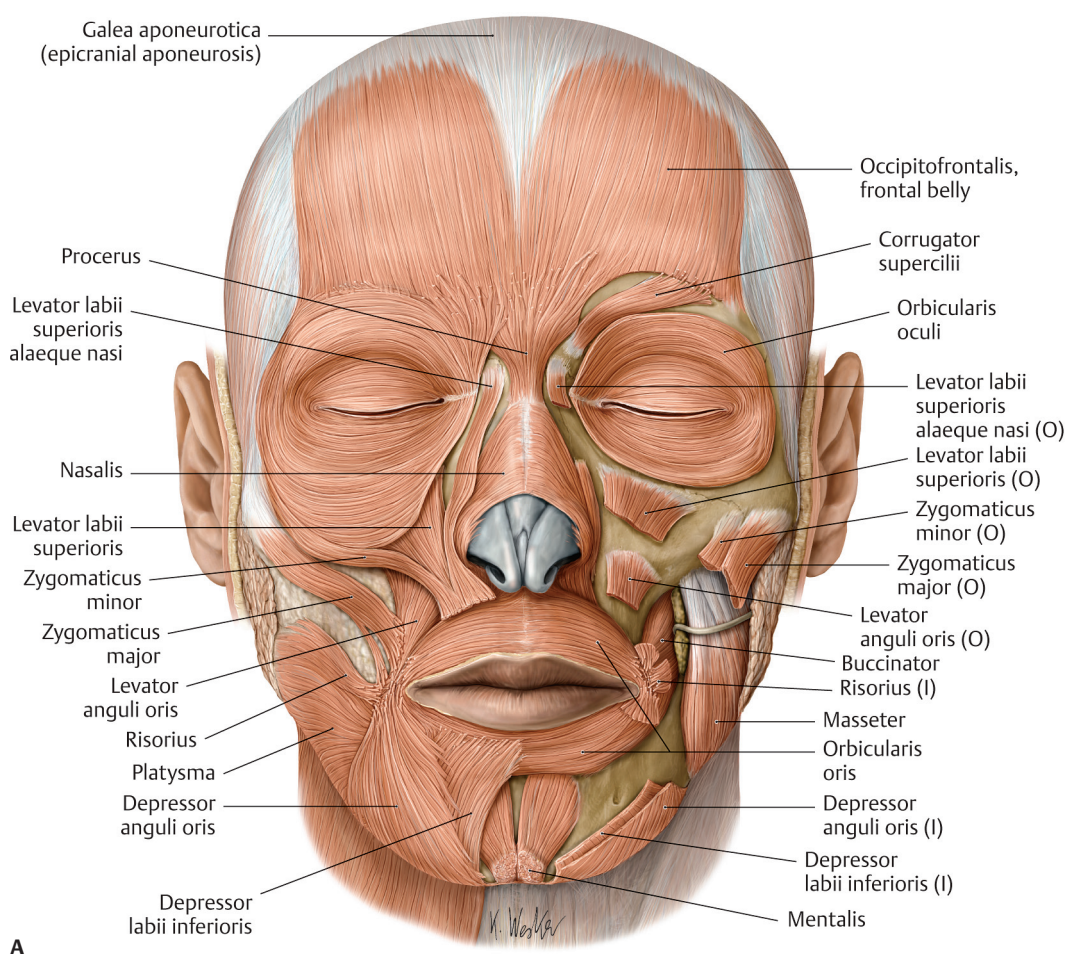


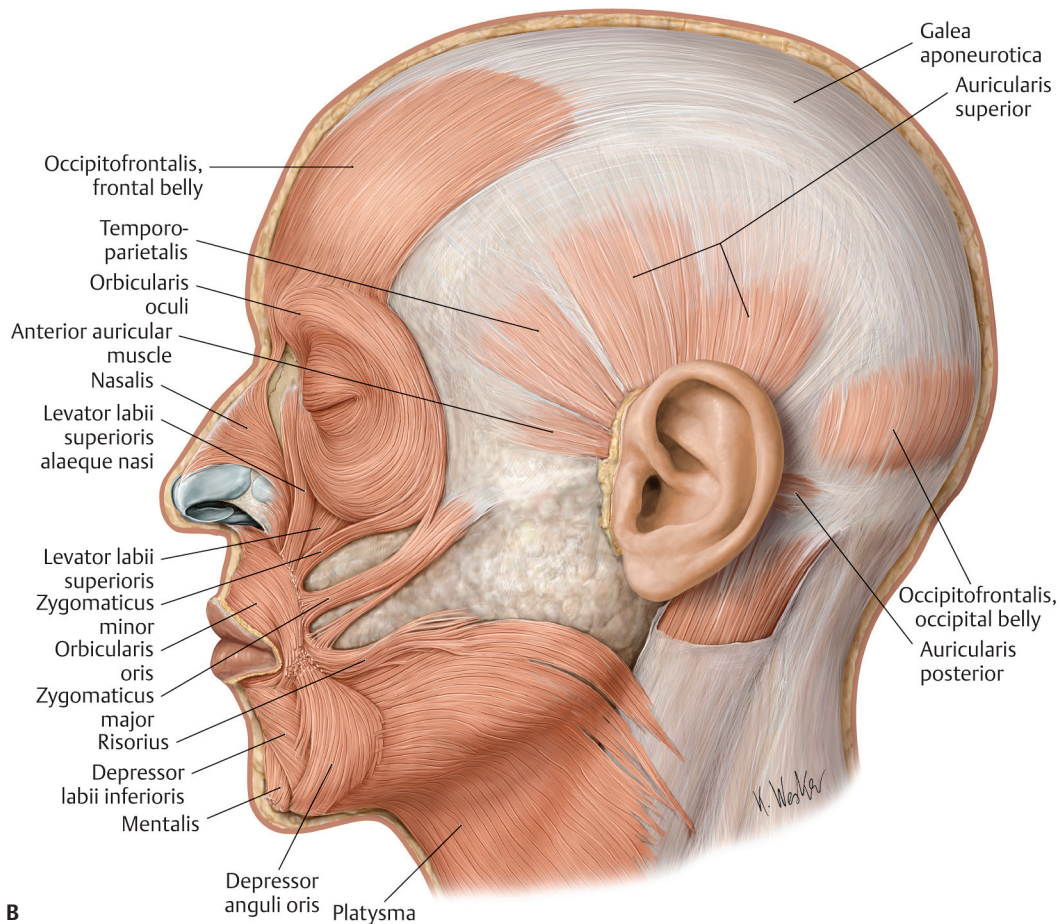
Fig. 9.1 (A) Muscles of facial expression. (From Atlas of Anatomy, © Thieme 2008, Illustration by Karl Wesker.)

dysphagia. These complications are dose and technique related, and may be avoided by injection of small volumes and using EMG guidance, when necessary. Systemic complications, including fatigue, generalized weakness, and nausea, are extremely rare, even when larger doses are used.⁴ However, patients who receive large and frequent doses are at risk for developing neutralizing antibodies to the toxin, which will render the patient resistant to future BoNT/A therapy.¹²

Horizontal Forehead Lines

Anatomy

The frontalis muscle elevates the brows and the skin of the forehead, resulting in horizontal lines often associated with aging (Figs. 9.1 and 9.2; Table 9.1). Although BoNT/A injection of the frontalis muscle reduces the appearance of horizontal facial lines, if used without concurrent injection of the brow depressors (see Glabellar Lines, below) it may have the undesirable effect of lowering the brows.



B

Fig. 9.1 (B) (Continued)



Fig. 9.2 Occipitofrontalis muscle. (From Atlas of Anatomy, © Thieme 2008, Illustration by Karl Wesker.)

Technique

Four to eight points (1.5–2.5 U BoNT/A per point) are injected in a curved horizontal line or two rows for a large forehead, crossing both the medial and lateral fibers at least 1.5 cm above the brow (**Fig. 9.3**). Most practitioners now inject less BoNT/A in the frontalis muscle than they have in the past, thereby avoiding the “frozen face” look associated with paralysis of the frontalis muscle. Rather than immobilization, the goal of treatment should be a more relaxed, natural appearance. Typical starting doses for women range between 6 and 15 U, with men usually requiring higher doses of 6 to >15 U.

Follow-Up

If inadequate correction of horizontal forehead rhytids or overarched brows is noted, additional BoNT/A may be injected a minimum of 7 days after the initial injections, at which time the expected effect of the initial BoNT/A should be achieved.

Complications

Keep in mind that the frontalis muscle is a brow elevator, so keep the injection sites well above the brow and keep doses low to decrease the risk of brow ptosis. Doses greater than 20 U are more likely to result in complications. Brow ptosis may be managed with an additional corrugator injection or injection of the depressor supercilii directly below the brow.

The medial fibers of the frontalis are usually stronger than the lateral fibers. Isolated injection of the medial fibers can result in the overarched “Spock eyebrow” caused by unopposed lateral fiber compensation to medial fiber injection. This phenomenon may also be seen following glabellar injections, whereby the weakened brow depressors, the corrugator and procerus, are unable to counteract the unopposed lateral frontal fibers. Low-dose injections to the upper lateral frontalis muscle will correct this undesirable effect.

Upper eyelid ptosis (blepharoptosis) may occur if the lateral injection is performed too close to the eyebrow, and diffusion occurs into the levator palpebralis superioris. This phenomenon may be avoided by applying digital pressure below the injection site to prevent migration of the bolus. Should blepharoptosis occur, it may be partially ameliorated with apraclonidine or phenylephrine ophthalmic drops, which stimulate Mueller’s muscle to elevate the upper eyelid. Most cases of blepharoptosis are mild to moderate and resolve within 2 to 3 weeks.¹³

Table 9.1 Muscles of Facial Expression: Forehead, Nose, and Ear

Muscle	Origin	Insertion^a	Main Action(s)^b
<i>Calvaria</i>			
1. Occipitofrontalis (frontal belly)	Epicranial aponeurosis	Skin and subcutaneous tissue of eyebrows and forehead	Elevates eyebrows, wrinkles skin of forehead
<i>Palpebral fissure and nose</i>			
2. Procerus	Nasal bone, lateral nasal cartilage (upper part)	Skin of lower forehead between eyebrows	Pulls medial angle of eyebrows inferiorly, producing transverse wrinkles over bridge of nose
3. Orbicularis oculi	Medial orbital margin, medial palpebral ligament; lacrimal bone	Skin around margin of orbit, superior and inferior tarsal plates	Acts as orbital sphincter (closes eyelids) • Palpebral portion gently closes • Orbital portion tightly closes (as in winking)
4. Nasalis	Maxilla (superior region of canine ridge)	Nasal cartilages	Flares nostrils by drawing ala (side) of nose toward nasal septum
5. Levator labii superioris alaeque nasi	Maxilla (frontal process)	Alar cartilage of nose and upper lip	Elevates upper lip, opens nostril
<i>Ear</i>			
6. Anterior auricular muscles	Temporal fascia (anterior portion)	Helix of the ear	Pull ear superiorly and anteriorly
7. Superior auricular muscles	Epicranial aponeurosis on side of head	Upper portion of auricle	Elevate ear
8. Posterior auricular muscles	Mastoid process	Convexity of concha of ear	Pull ear superiorly and posteriorly

^aThere are no bony insertions for the muscles of facial expression.

^bAll muscles of facial expression are innervated by the facial nerve (cranial nerve VII) via temporal, zygomatic, buccal, mandibular, or cervical branches arising from the parotid plexus.

(From THIEME Atlas of Anatomy: Head and Neuroanatomy, © Thieme 2007.)

Glabellar Lines

Anatomy

The glabellar complex is composed of the procerus, corrugator supercilii, depres-

sor supercilii, and orbicularis oculi, all of which are brow depressors (**Figs. 9.1 and 9.4**). The corrugator supercilii also draws the brows medially, resulting in vertical glabellar lines. Different glabellar



Fig. 9.3 Injection of frontalis muscle.

“frown patterns” may occur, depending on the relative contribution of the vertical and horizontal vectors.

Technique

Five to seven injection points are identified in a V-shaped pattern, with the narrow point immediately cranial to the insertion of the procerus muscle at the nasion. A total of 10 to 30 U are commonly used in women and 20 to 40 U in men. As with frontalis injections, most clinicians now inject less than they did in the past. To avoid inadvertent injection into the frontalis, the upper injections should be placed no more than 1 cm superior to the orbital rim. To

avoid brow ptosis, injection lateral to the midpupillary line should be avoided (**Fig. 9.5**).

Follow-Up

If inadequate correction of glabellar rhytids or overarch of the brows is noted, additional BoNT/A may be injected a minimum of 7 days after the initial injections, at which time the expected effect of the initial BoNT/A should be achieved.

Complications

“Spock eyebrow” can occur, whereby the weakened brow depressors, the corrugator and procerus, are unable to coun-

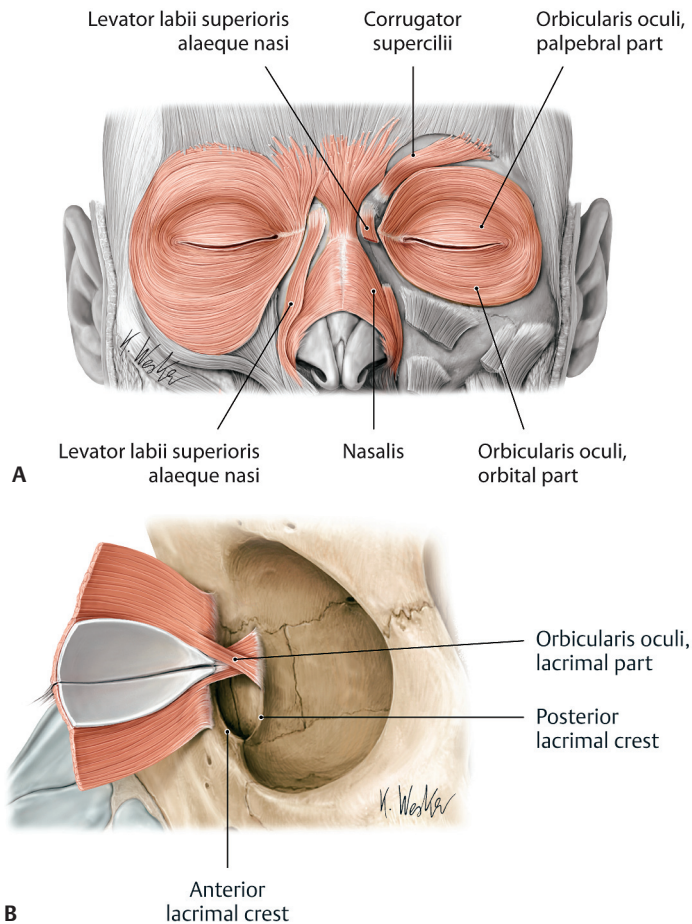


Fig. 9.4 (A,B) Muscles of facial expression in the periorbital anatomy. (From THIEME Atlas of Anatomy: Head and Neuroanatomy, © Thieme 2007, Illustration by Karl Wesker.)

teract the unopposed lateral frontal fibers. The management of this problem is low-dose injections to the upper lateral frontal muscle.

Patients with narrow brows should receive fewer injections and lower doses than patients with broad brows.

Upper eyelid ptosis (blepharoptosis) may occur if the injections are performed too close to the eyebrow, and diffusion occurs into the levator palpebral superi-

oris. This phenomenon may be avoided by grasping the corrugator muscle during injection or by applying digital pressure below the injection site to prevent migration of the bolus. Blepharoptosis may be partially ameliorated with apraclonidine or phenylephrine ophthalmic drops, which stimulate Mueller's muscle to elevate the upper eyelid. Most cases of blepharoptosis are mild to moderate and resolve within 2 to 3 weeks.^{6,13}



Fig. 9.5 (A,B) Injection of the glabellar complex.

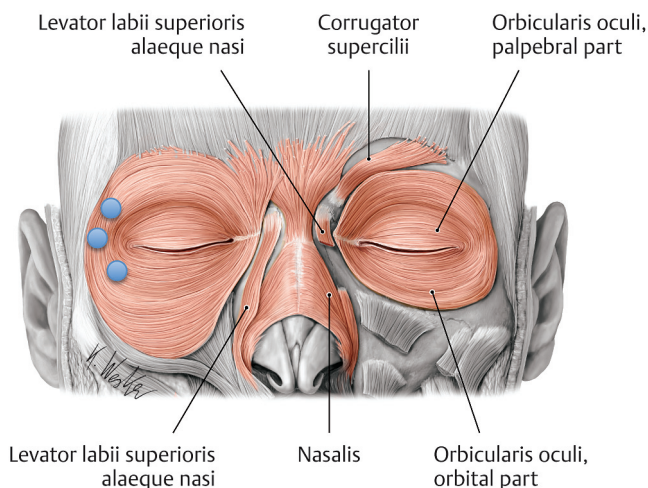


Fig. 9.6 Injection of the lateral orbicularis oculi. (From THIEME Atlas of Anatomy: Head and Neuroanatomy, © Thieme 2007, Illustration by Karl Wesker.)

Brow Lift

Hyperfunction of the brow depressors results in a lowered brow, a facial gesture that may be associated with emotional states such as anger, fatigue, frustration, and anxiety. The concept of the “Botox brow lift” is based on selective weakening of the brow depressors, resulting in unopposed brow elevation by the frontalis muscle. Several investigators have documented 1- to 4.8-mm elevation of the brow following injection of the brow depressors or medial frontalis fibers. This effect may be achieved with the traditional glabellar injection pattern (**Fig. 9.5**), but may also be augmented by lateral orbicularis oculi injections performed below the brow, but superior and lateral to the orbital rim (**Fig. 9.6**). As mentioned above, selective weakening of the medial frontalis fibers may also result in increased resting tone of the lateral fibers, thereby resulting in

elevation of the middle and lateral brow. These techniques are also useful for those patients with eyebrow asymmetry as a result of trauma, surgery, and facial nerve paralysis.

Periocular Lines (“Crow’s Feet”)

Anatomy

The orbicularis oculi muscle originates from the nasal process of the frontal bone, the lacrimal bone, and the medial palpebral ligament. It is divided into three concentric portions: lacrimal (innermost), palpebral, and orbital (outermost) (**Fig. 9.4**). The fibers of the orbital portion form a complete ellipse around the eye, with the outermost fibers blending with the frontalis, corrugator, and masseter. Contraction of the lateral orbital fibers of the orbicularis oculi results in the characteristic radial periocular lines known as “crow’s feet.” These



Fig. 9.7 Injection of the orbicularis oculi muscle.

rhytides frequently develop earlier in fair-skinned individuals, smokers, and those with photodamage.

Technique

Two to five injection sites no closer than 1 cm lateral to the lateral orbital rim are used to inject a total of 10 to 30 U in women and 20 to 30 U in men (**Fig. 9.7**). Many experienced clinicians are now injecting increased amounts of BoNT/A in men. These injections are frequently used in combination with malar volume augmentation.

Follow-Up

If inadequate correction of periocular lines is noted, additional BoNT/A may be injected a minimum of 7 days after

the initial injections, at which time the expected effect of the initial BoNT/A should be achieved.

Complications

Special care must be paid to avoid disrupting the small superficial blood vessels in the periorbital region. Placing the patient in a prone position and using proper lighting will help the injector to avoid bruising. Superficial deep dermal injections rather than intramuscular injection may also reduce the risk of bruising.

Extensive preinjection counseling regarding the minimal effect on deep lines, upper eyelid hooding, and lower lid changes best treated with fillers, skin resurfacing techniques, or surgery is critically important to avoid unrealistic

patient expectations regarding BoNT/A treatment in this dynamic, complex anatomic region.¹⁴

Hypertrophic Pretarsal Orbicularis

Anatomy

Smiling decreases the perceived size of the palpebral aperture. Some patients seek a more rounded-appearing eye, both at rest and during smiling. The practitio-

ner can achieve this appearance by injecting the inferior pretarsal orbicularis oculi muscle (**Fig. 9.8**). These injections also decrease lower eyelid fine lines, but not deep lines or dermatochalasis.

Technique

These injections are administered subcutaneously along the tarsal plate. The patient is asked to look up, and the needle is placed several millimeters below

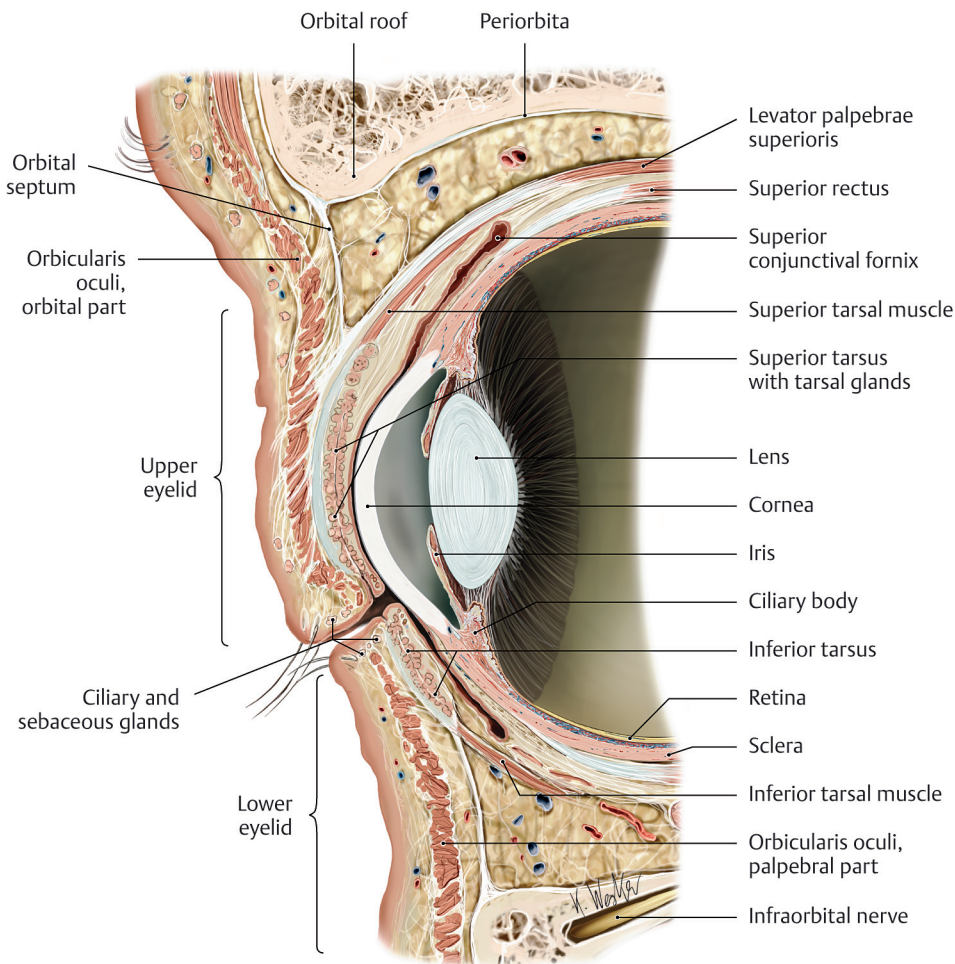


Fig. 9.8 Orbicularis oculi muscle. (From THIEME Atlas of Anatomy: Head and Neuroanatomy, © Thieme 2007, Illustration by Karl Wesker.)



Fig. 9.9 Injection of the inferior pretarsal orbicularis oculi muscle.

the lash line (**Fig. 9.9**). The injections should not be given any more medial than the midpupillary line to prevent epiphora from too much orbicularis weakening. No more than 2 U of BoNT/A should be injected per eyelid.

Follow-Up

If inadequate correction of the hypertrophic pretarsal orbicularis is noted, additional BoNT/A may be injected a minimum of 7 days after the initial injections, at which time the expected effect of the initial BoNT/A should be achieved.

Complications

Care must be taken to avoid small vessels to prevent bruising. These injections should not be given to patients who fail

the “snap test” to evaluate laxity of the tarsal plate, patients who have had lower eyelid ablative resurfacing, or patients with dry eyes or scleral show.⁷

Nasalis (“Bunny Lines”)

Anatomy

“Bunny lines” are dynamic vertically oriented rhytids on the lateral aspect of the nasal dorsum that may extend to the lower eyelids and cheeks when the patient smiles or laughs. These lines result from the contraction of the nasalis muscle, which is a U-shaped muscle with transverse fibers extending across the nasal dorsum, and vertical fibers running down the lateral dorsum (**Fig. 9.4**). These fibers move the nose and control the size of the nostrils.

Technique

A dose of 2.5 to 5 U is injected into the midportion of the nasalis muscle, which

is located halfway between the dorsum of the nose and the face of the maxilla over the nasal bone (**Fig. 9.10**).

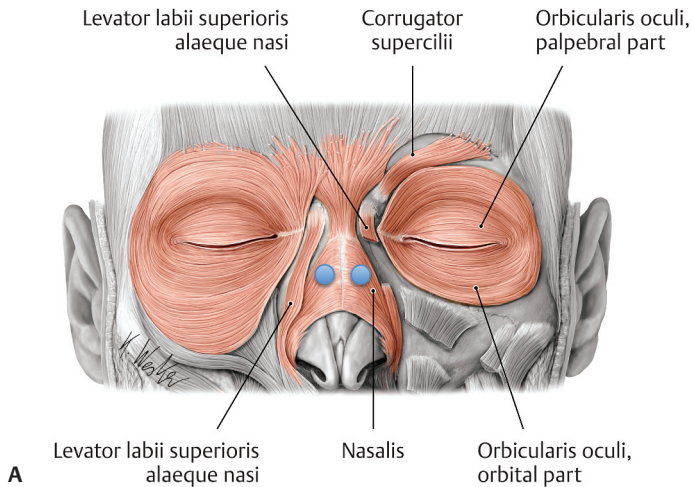


Fig. 9.10 (A) Injection of the nasalis muscle. (From THIEME Atlas of Anatomy: Head and Neuroanatomy, © Thieme 2007, Illustration by Karl Wesker.) **(B)** Drawing of the injection site.

Follow-Up

If inadequate correction of nasalis lines is noted, additional BoNT/A may be injected a minimum of 7 days after the initial injections, at which time the expected effect of the initial BoNT/A should be achieved.

Complications

Pain at the injection sites and bruising may occur. The clinician must keep volumes small to prevent diffusion to the medial rectus muscle, levator labii superioris, or the levator labii alaeque nasi.^{7,14}

Perioral Lines*Anatomy*

The orbicularis oris is a sphincter muscle whose fibers mediate the closure and protrusion of the lips (**Fig. 9.11E; Table 9.2**). Perioral lines, also called “smoker’s lines” or “lipstick lines,” result from pleating of the skin during contraction of the orbicularis oris muscle.

Technique

Low-dose injections are given on each side of the upper lip, 5 to 8 mm above the mucocutaneous junction (**Fig. 9.12**). A total of two or four injections may be administered, with a total of 2 to 5 U, depending on the horizontal length of the lip and the severity of the lines. These lines can also be treated with small amounts of filler agents, or laser or chemical peels in the areas of the deepest lines.

Follow-Up

If inadequate correction of perioral lines is noted, additional BoNT/A may be injected a minimum of 7 days after the initial injections, at which time the expected effect of the initial BoNT/A should be achieved.

Complications

Only small amounts of toxin can be given or patients will develop lip incompetence, drooling, or dysarthria. The lateral injection points should be at least 1.5 cm away from the oral commissure. These injections are relatively contraindicated in professional singers, actors, and wind instrumentalists.¹⁴

Excessive Gingival Display (“Gummy Smile”)*Anatomy*

Excessive gingival display is related to hyperfunction of the levator labii superioris alaeque nasalis, levator labii superioris, levator anguli oris, zygomaticus major and minor, and the depressor septi nasi muscles in conjunction with individual anatomic characteristics such as size and configuration of the upper lip and maxilla.

Technique

Due to the complex interplay of these muscles, conservative treatment is aimed at weakening the levator labii superioris alaeque nasalis muscle, by injecting 1 to 2.5 U at the inferior edge of the nasal

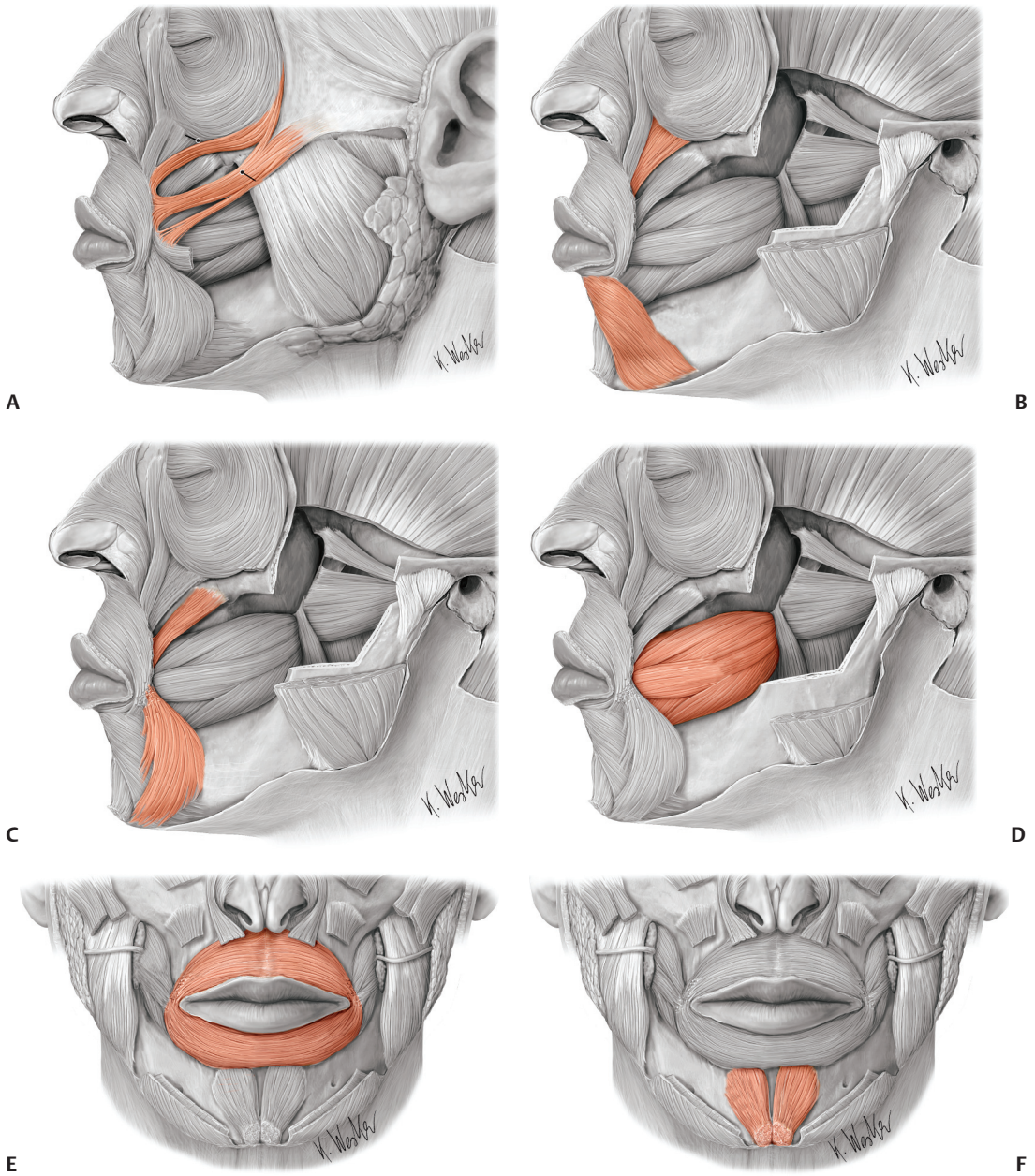


Fig. 9.11 (A–F) Muscles of the mouth. (From Atlas of Anatomy, © Thieme 2008, Illustration by Karl Wesker.)

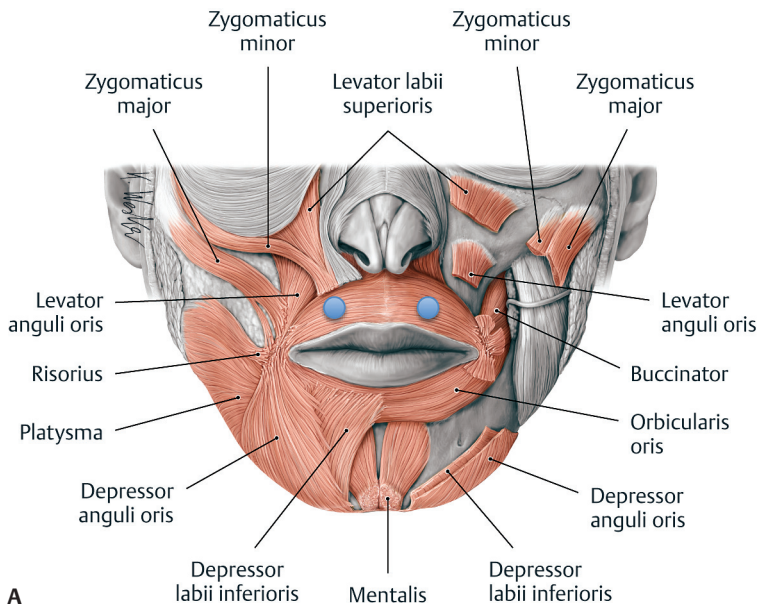
Table 9.2 Muscles of Facial Expression: Mouth and Neck

Muscle	Origin	Insertion^a	Main Action(s)^b
<i>Mouth</i>			
1. Zygomaticus major	Zygomatic bone (lateral surface, posterior part)	Skin at corner of the mouth	Pulls corner of mouth superiorly and laterally
2. Zygomaticus minor		Upper lip just medial to corner of the mouth	Pulls upper lip superiorly
3. Levator labii superioris alaeque nasi	Maxilla (frontal process)	Alar cartilage of nose and upper lip	Elevates upper lip, opens nostril
4. Levator labii superioris	Maxilla (frontal process) and infraorbital region	Skin of upper lip, alar cartilages of nose	Elevates upper lip, dilates nostril, raises angle of the mouth
5. Depressor labii inferioris	Mandible (anterior portion of oblique line)	Lower lip at mid-line; blends with muscle from opposite side	Pulls lower lip inferiorly and laterally
6. Levator anguli oris	Maxilla (below infraorbital foramen)	Skin at corner of the mouth	Raises angle of mouth, helps form nasolabial furrow
7. Depressor anguli oris	Mandible (oblique line below canine, premolar, and first molar teeth)	Skin at corner of the mouth; blends with orbicularis oris	Pulls angle of mouth inferiorly and laterally
8. Buccinator	Mandible, alveolar processes of maxilla and mandible, pterygomandibular raphe	Angle of mouth, orbicularis oris	Presses cheek against molar teeth, working with tongue to keep food between occlusal surfaces and out of oral vestibule; expels air from oral cavity/resists distension when blowing <i>Unilateral:</i> draws mouth to one side
9. Orbicularis oris	Deep surface of skin Superiorly: maxilla (median plane) Inferiorly: mandible	Mucous membrane of lips	Acts as oral sphincter • Compresses and protrudes lips (e.g., when whistling, sucking, and kissing) • Resists distension (when blowing)
<i>Risorius</i>			
	Fascia over masseter	Skin of corner of the mouth	Retracts corner of mouth as in grimacing
10. Mentalis	Mandible (incisive fossa)	Skin of chin	Elevates and protrudes lower lip
<i>Neck</i>			
Platysma	Skin over lower neck and upper lateral thorax	Mandible (inferior border), skin over lower face, angle of mouth	Depresses and wrinkles skin of lower face and mouth; tenses skin of neck; aids in forced depression of the mandible

^aThere are no bony insertions for the muscles of facial expression.

^bAll muscles of facial expression are innervated by the facial nerve (cranial nerve VII) via temporal, zygomatic, buccal, mandibular, or cervical branches arising from the parotid plexus.

(From THIEME Atlas of Anatomy: Head and Neuroanatomy, © Thieme 2007.)



A



B

Fig. 9.12 (A) Injection of orbicularis oris. (From THIEME Atlas of Anatomy: Head and Neuroanatomy, © Thieme 2007, Illustration by Karl Wesker.) **(B)** Drawing of the injection site.

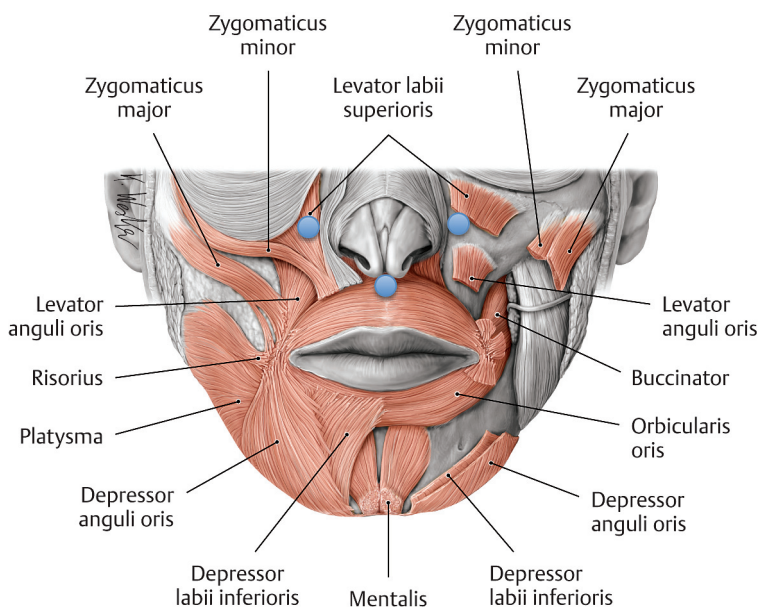


Fig. 9.13 Muscles of the mouth. (From THIEME Atlas of Anatomy: Head and Neuroanatomy, © Thieme 2007, Illustration by Karl Wesker.)

bone at the junction of the maxilla. An alternative treatment target is the depressor septi nasi, which is injected with 2 to 3 U at the base of the columella (**Fig. 9.13**).

Follow-Up

If inadequate correction of excessive gingival display is noted, additional BoNT/A may be injected a minimum of 7 days after the initial injections, at which time the expected effect of the initial BoNT/A should be achieved.

Complications

Too much toxin will cause too much weakness of the levator system and can result in upper lip ptosis, smile asymmetry, and excessive lengthening of the

upper lip. These injections are relatively contraindicated in professional singers, actors, and wind instrumentalists as well.^{14,15}

Melomental Folds (“Marionette Lines”)

Anatomy

Melomental folds are vertical lines that extend from the modiolus to the lateral mentum due to the downward pull of the triangular-shaped depressor anguli oris (DAO) muscles (**Fig. 9.11C**; **Table 9.2**). Although they may be treated with soft tissue augmentation alone, the addition of BoNT/A will extend the life of the augmentation and decrease the unhappy appearance of the downward-turned lip.



Fig. 9.14 Injection of the depressor anguli oris.

Technique

The patient is asked to pull the lower lip in a downward direction so that the DAO can be palpated. It should be injected with 5 U of BoNT/A at the midpoint between the lip edge and the lower border of the mandible (**Fig. 9.14**). If the injection is placed too high, there may be significant weakening of the orbicularis oris.

Follow-Up

If inadequate correction of melomental folds is noted, additional BoNT/A may be injected a minimum of 7 days after the initial injections, at which time the expected effect of the initial BoNT/A should be achieved.

Complications

If the injection is placed too high, drooling and dysarthria can result from weakening of the orbicularis oris. These injections are relatively contraindicated in professional singers, actors, and wind instrumentalists.¹⁴

Mental Crease and *Peau d'Orange*

Anatomy

The mentalis is a perpendicular muscle that covers the chin and inserts transversely in the dermis of the lower lip (**Fig. 9.11F**; **Table 9.2**). Contraction of the mentalis can produce a prominent mental crease or the dimpled appearance termed *peau d'orange*. These findings



Fig. 9.15 Injection of the mentalis muscle.

may be increasingly noticeable as the subcutaneous fat and dermal collagen is lost over time.

Technique

A total of 4 to 5 U in women and 6 to 10 U in men are injected either with one midline injection or bilaterally in the lower third of the mentalis muscles (**Fig. 9.15**). BoNT/A treatment may be combined with fillers with good effect.

Follow-Up

If inadequate correction of the mental crease or *peau d'orange* is noted, additional BoNT/A may be injected a minimum of 7 days after the initial injections,

at which time the expected effect of the initial BoNT/A should be achieved.

Complications

If the injection is placed above the mental crease, there may be weakening of the orbicularis oris producing drooling or dysarthria.^{9,14}

Vertical Platysmal Bands

Anatomy

These vertical neck bands are caused by the edge of a hyperactive platysma muscle. The platysma is a thin, broad muscle that originates from the border of the mandible/SMAS (superficial

musculo-aponeurotic system) and inserts in the clavicular region (**Fig. 9.1**). These bands are most prominent during smiling, speaking, or other social gestures. Their appearance may be exaggerated after a face-lift, especially if platysmal plication is not performed.

Technique

The anterior border and posterior borders of the muscles are outlined on the skin. Sequential horizontal lines are drawn starting approximately 1 cm below the mandible, and repeated every 1.5 cm. Either small amounts (2.5 U per 0.1 cc) are given directly into the edge of the platysma every 1 to 2 cm, or, using EMG guidance, the muscle can be entered along the long axis, and then injected as the needle is withdrawn (**Fig. 9.16**). Usually, a total of 10 to 15 U per muscle is administered.

Follow-Up

If inadequate correction of vertical platysmal bands is noted, additional BoNT/A may be injected a minimum of 7 days after the initial injections, at which time the expected effect of the initial BoNT/A should be achieved.

Complications

If too much toxin is given, or if the BoNT/A is injected too deeply, the strap muscles may be weakened. This may result in poor elevation of the larynx with swallowing, thereby producing dysphagia.

The most important area to avoid is the cervicomental junction, due to the close proximity of the swallowing musculature. The toxin may also migrate medially to the cricothyroid muscle, causing pitch changes during voicing.⁹

Horizontal Platysmal Bands (“Necklace Bands”)

Anatomy

Because these lines are often related to repeated flexion of the obese neck, they frequently cannot be softened or removed with BoNT/A injection. However, some of these lines may be caused by attachments of the SMAS within the neck, which represents an appropriate target for BoNT/A treatment.

Technique

The injection technique is similar to that described for vertical platysmal bands, but the injections are often given in the deep intradermal plane along the lines, using an interrupted technique. A total of 10 to 15 U are injected.

Follow-Up

If inadequate correction of the horizontal platysmal bands is noted, additional BoNT/A may be injected a minimum of 7 days after the initial injections, at which time the expected effect of the initial BoNT/A should be achieved. However, BoNT/A failure to smooth the lines likely indicates that the lines are not the result of insertion of the SMAS.



A



B

Fig. 9.16 (A) Injection of the platysma muscle. (B) Drawing of the injection site.

Complications

The same complications described in the vertical platysmal bands section apply to injections for horizontal platysmal bands.

■ Conclusion

The use of BoNT for the reduction of hyperfunctional facial lines is a commonly performed nonsurgical facial rejuvenation procedure because of the remarkable safety, reliability, and patient satisfaction associated with its use over the

past decade. Current trends in facial rejuvenation reveal increasing use of adjunctive procedures, including volume augmentation and skin resurfacing in conjunction with BoNT treatment. The future of facial aesthetic medicine and surgery will undoubtedly bring new formulations of BoNT, as well as new, minimally invasive procedures into the clinician's armamentarium. However, safe and effective administration of BoNT will always depends on a thorough understanding of the muscular and vascular anatomy of the face and neck, as well as proper patient counseling regarding the anticipated aesthetic outcome.



Video 11 Cosmetic: Crow's Feet

The patient is asked to squint so that the areas of maximum line formation may be seen. Then, three injections of toxin (2.5 U/0.1 cc) along the orbital rim at least 1 cm from the lateral rectus attachment.



Video 12 Cosmetic: Frown Lines

You see in this video a “Blitzer” safety triangle drawn. If you place one point between the medial portion of the brows and then another at 1 cm above the superior orbital rim at the midpapillary line bilaterally, a triangle can be drawn. Anything within this triangle is safe to inject. Leaving a bit of lateral frontalis muscle allows for some mimetic action and expressivity. You see in this video the corrugator muscle being injected within the triangle to eliminate frown lines. Injection of 2.5 U/0.1 cc is given in five places.



Video 13 Cosmetic: Lower Eyelid

These injections are given just subcutaneously along the tarsal plate. They shouldn't be given medial to the midpupillary line to prevent weakening of the pumping action of the lower lid and producing epiphora. These injections will reduce the lower lid lines and make the lid opening rounder. Injections are 1.0 U/0.05 cc in two places along the lower lid.



Video 14 Cosmetic: Mentalis

These injections treat the *peau d'orange* skin changes. Each mentalis muscle is injected with 2.5 to 5 U/0.1 cc. The injections should be given no higher than halfway superior from the inferior border of mandible to the upper border of the lower lip. Above this line threatens to weaken the orbicularis oris and may produce drooling or dysarthria.



Video 15 Cosmetic: Platysma

The anterior edge and posterior edge of the platysma muscles are marked. A “ladder” of horizontal lines is drawn approximately 2 cm apart. Using an EMG needle, the ladder lines are skewered observing for good muscle EMG activity and 2.5 U/0.1 cc is injected in each pass as the needle is removed. For large anterior bands, the band can be grasped between fingers and extra toxin injected into the bands.

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Upper and Lower Esophageal Spasm

Nwanmegha Young and Brian E. Benson

Dysphagia, or impaired swallowing ability, is a very common disorder that can have adverse effects on quality of life and overall health. Although over 20% of the adult population experiences dysphagia several times a month,¹ the impact on overall health and quality of life can range from minimal, in the case of mild dysphagia, to severe and life-threatening, in the case of severe dysphagia. Dysphagia may result from dysfunction of any of the components involved in the complex neuromuscular interaction of swallowing. There are two major categories of dysphagia: (1) *oropharyngeal*, which refers to difficulty in the passage of a food bolus from the oropharynx into the esophagus; and (2) *esophageal*, which refers to disturbances of the passage of the food bolus within the esophagus itself.² Hyperfunction of any of the muscles involved in

swallowing is a frequent cause of dysphagia, although in most cases of moderate or severe dysphagia, there are multiple, significant deficits related to muscle strength, coordination, and sensation. With regard to isolated hyperfunctional dysphagia, dysfunction of the cricopharyngeal (CP) muscles (failure to relax) is the most common cause of oropharyngeal dysphagia, and hypertonicity of the lower sphincter is associated with esophageal dysphagia.^{3,4}

Treatment of these disorders depends on the etiology of the dysphagia (stroke, neurodegenerative disease, congenital disorders, high vagal lesions, postlaryngectomy, etc.), and may include surgery, medications, or swallowing therapy, or some combination of them. When the main cause of dysphagia is hyperfunctional muscles, chemodenervation with botulinum neurotoxin (BoNT) is a rea-

sonable treatment option. This chapter reviews the anatomy, physiology, and management of hyperfunctional swallowing disorders that may affect the pharyngoesophageal phase of swallowing.

Failure of the upper esophageal sphincter (UES) to relax, termed cricopharyngeal achalasia (CA), can cause severe dysphagia. CA is a characteristic symptom in a variety of neurologic disorders including lesions of the skull base and stroke. UES hypertonicity is also associated with distal esophageal reflux,⁵ so in mildly symptomatic patients, treatment with proton pump inhibitors may be effective. Clinical symptoms of CA include globus sensation and dysphagia. In laryngectomized patients, CA will also reliably cause difficulty with tracheoesophageal puncture (TEP) phonation. For this reason, most surgeons now perform CP myotomy at the time of the laryngectomy. In newborns, an esophagram confirms the diagnosis. In adults, however, the diagnosis is best aided by manometry or electromyography (EMG). However, equivocal findings with these testing modalities, which have significant technical aspects, do not rule out CA.

Cricopharyngeal achalasia can be managed with a variety of treatments, including mechanical dilatation, pharyngeal plexus neurectomy, and CP myotomy. The definitive treatment of CA remains CP myotomy, via either an endoscopic or open transcervical approach.⁶ Injection of BoNT into the cricopharyngeus muscle, either percutaneously or endoscopically under general anesthesia, has shown benefit in 70 to 100% of patients

in noncontrolled series.⁷ The effects of the injection lasted between 4 months and 1 year. Therefore, BoNT injection is not only an attractive nonsurgical alternative treatment for CA but also a useful tool to identify which patients could be expected to experience benefit from CP myotomy. An important exception is patients with fibrosis of the CP, who will not experience benefit from BoNT, but may benefit from dilation or myotomy.

Lower esophageal sphincter (LES) spasm, referred to as achalasia, esophageal achalasia, and cardiospasm, is a primary esophageal motility disorder characterized by failure of a hypertensive LES to relax and the absence of esophageal peristalsis. These abnormalities cause a functional obstruction at the gastroesophageal junction, leading to dysphagia, regurgitation, weight loss, and occasionally chest pain. These symptoms may also be mimicked by neoplasm and infection (Chagas disease). Treatments for achalasia include medications, balloon dilation, and myotomy. Calcium channel blockers and nitrates have shown short-term efficacy, but their use is limited by side effects, including headache, dizziness, hypotension, and peripheral edema.⁸ Although the durability of response in patients undergoing myotomy or balloon dilation techniques is superior that in patients who undergo BoNT injection, intrasphincteric injection of BoNT has been demonstrated to be an extremely safe and effective treatment for those patients who are not good surgical candidates, or who prefer to avoid surgical risks.⁹

■ **Workup**

Evaluation of dysphagia requires a thorough history and physical examination, often including fiberoptic evaluation of the oropharynx, endolarynx, and hypopharynx, and of the esophagus and stomach. Additional studies are listed in **Table 10.1**.

Upper Esophageal Sphincter

The radiographic hallmark of CP achalasia, the “cricopharyngeal bar,” represents the protrusion of the CP muscle into the digestive tract as the bolus of radiopaque material passes through the UES. However, the absence of a CP bar does not rule out the possibility of UES hyperfunction if the history and physical examination findings are suggestive (**Fig. 10.1**). Fiberoptic pharyngoscopy may reveal pooling of secretions with the pyriform sinus region on the affected side. Electromyography (EMG) studies may reveal the lack of cessation of electrical activity, although a decrease in signal is usually noted during swallowing, even in patients with CP achalasia.



Fig. 10.1 Cricopharyngeal bar.

Lower Esophageal Sphincter

Esophageal manometry frequently reveals high resting LES pressure, incomplete relaxation of the LES during swallowing, and absent esophageal peristalsis. A barium esophagram shows a proximal dilated esophagus. The distal esophagus

Table 10.1 Studies Used in the Evaluation of Dysphagia

<i>Radiologic studies</i> Modified barium swallow Barium esophagram
<i>Functional evaluation</i> Flexible fiberoptic evaluation of swallowing (with or without) sensory testing Manometry
<i>Nerve studies</i> Electromyography

is narrowed and classically described as resembling a bird's beak.

■ Anatomy and Physiology

The esophagus forms a muscular conduit that connects the hypopharynx to the stomach. It is approximately 18 to 26 cm in length and topographically is divided into three regions: cervical, esophageal, and abdominal. The upper or cervical segment is composed of striated muscle, whereas the lower or abdominal part is composed of smooth muscle. The esophageal region is a mixed transition zone composed of both muscle types. The UES and LES, in conjunction with the esophagus, are responsible for antegrade transport of nutrients and for preventing the retrograde transport of gastric contents. Hypertonicity, that is, decreased or absent relaxation, in these zones, leads to dysphagia

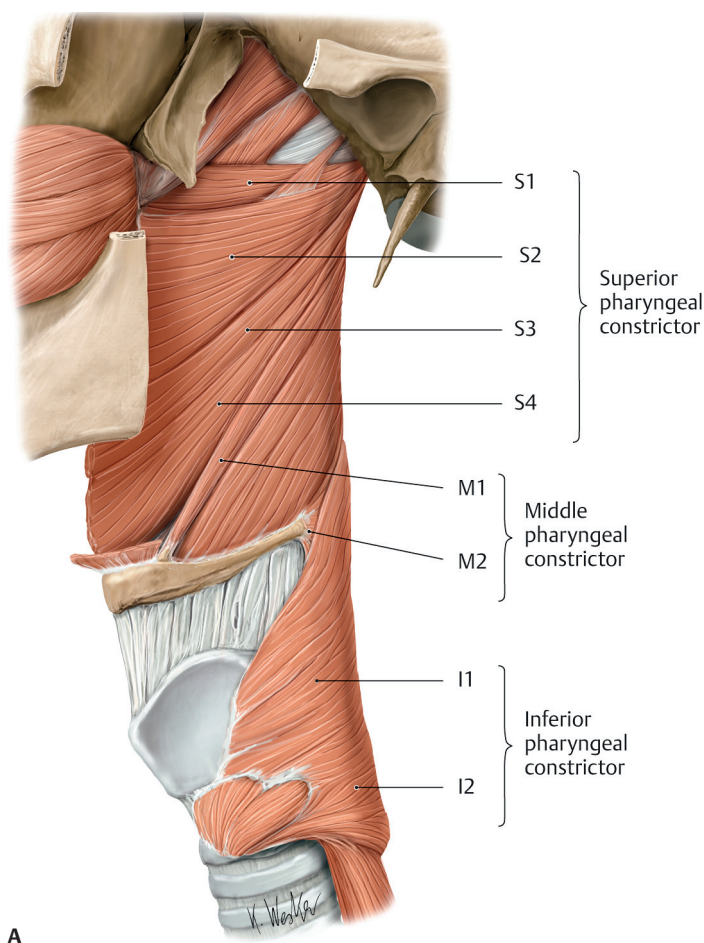
Upper Esophageal Sphincter

At each end of the esophagus there lies high-pressure zones.^{10,11} The UES is a 2- to 4-cm high-pressure zone at the junction of the hypopharynx and the esophagus (**Fig. 10.2**). The most prominent component of the UES is the cricopharyngeus muscle, which constitutes the lower third of the UES. The upper two thirds of the UES comprises the lower portion of the inferior pharyngeal constrictor. The fibers of the cricopharyngeus muscle originate and insert in the dorsolateral aspect of the cricoid cartilage, which defines the anterior aspect

of the UES. Although the innervation of the cricopharyngeus muscle remains a matter of debate, the most prominent contributions are from the vagus and glossopharyngeal nerves as well as the sympathetic nerve fibers.^{12–14} Innervation of the cricopharyngeus muscle is ipsilateral; therefore, the two halves of the cricopharyngeus muscle function independently. Acetylcholine is the primary neurotransmitter, thereby making the UES an attractive target for BoNT therapy in cases of hypertonicity. The cricopharyngeus muscle is unique among the muscles of the neck, in that it maintains a high intraluminal pressure during respiration and speech, relaxing only during deglutition.

Lower Esophageal Sphincter

The LES, also referred to as the gastroesophageal sphincter, cardiac sphincter, or esophageal sphincter, is located at the junction of the esophagus and the stomach. It has intrinsic (esophageal) and extrinsic (diaphragmatic) components (**Fig. 10.3**). Lower esophageal spasm or achalasia is a primary esophageal motility disorder characterized by failure of a hypertensive LES to relax and the absence of esophageal peristalsis. These abnormalities cause a functional obstruction at the gastroesophageal junction, leading to esophageal dysphagia, regurgitation, and weight loss. LES pressure and relaxation are regulated by excitatory (e.g., acetylcholine, substance P) and inhibitory (e.g., nitric oxide, vasoactive intestinal peptide) neurotransmitters. Patients with LES achalasia lack nonadrenergic,



A

Fig. 10.2 (A) Upper esophageal sphincter. (From Atlas of Anatomy, © Thieme 2008, Illustration by Karl Wesker.)

noncholinergic, inhibitory ganglion cells, causing an imbalance in excitatory and inhibitory neurotransmission.^{3,4} The result is a hypertensive nonrelaxed esophageal sphincter.

■ Upper Esophageal Sphincter Technique

Percutaneous

The patient is placed in the supine position. The surgeon stands at the side of the patient and rotates the larynx with

one hand while using the contralateral hand to pass a Teflon-coated hollow EMG recording needle through the skin and into the cricopharyngeus muscle. Entry into the cricopharyngeus muscle is confirmed by the EMG's demonstrating activity during rest and relaxation during swallowing, even in hyperkinetic states. The effective amount injected is usually 20 to 40 units (U) on each side.

Endoscopic

Under general anesthesia, a laryngoscope is positioned in the post cricoid

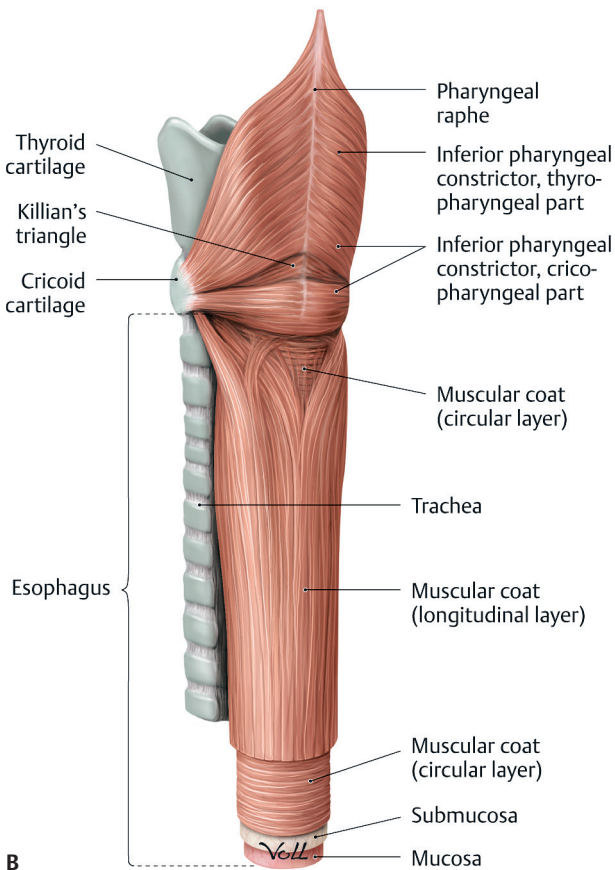


Fig. 10.2 (B) Upper esophageal sphincter. (From Atlas of Anatomy, © Thieme 2008, Illustration by Marcus Voll.)

region and placed in suspension. A bivalved laryngoscope, with sufficient length to expose the upper esophageal sphincter, is optimal for visualization. Because the cricoid cartilage is pushed anteriorly with the positioning of the scope, the cricopharyngeal muscle comes into view as a posterior bulky crescent at the cricopharyngeal inlet. This is similar to the placement of a laryngoscope for repair of a Zenker's diverticulum. A blunt tip probe is used to palpate the horizontally oriented muscle to confirm that the correct area is exposed. If the scope is not placed deeply enough, the inferior constrictor muscle may be inadvertently injected instead of the cricopharyngeus, and this

would produce a worsening of the patient's dysphagia.

Once the cricopharyngeal muscle is verified, it is injected under direct visualization. Laryngeal injection needles can be used or, alternatively, a butterfly needle with its wings cut off can be used to deliver the toxin. Typically, 1 or 2 areas of the muscle are injected with BoNT on each side of the posterior portion of the muscle in the 5 o'clock and 7 o'clock positions. The anterior aspect of the muscle should not be injected, as this may cause stridor due to paralysis of the posterior cricoarytenoid muscle. The amount injected varies widely between authors, from 5 u to 100 u, with typical doses ranging from 50 to 100 u.

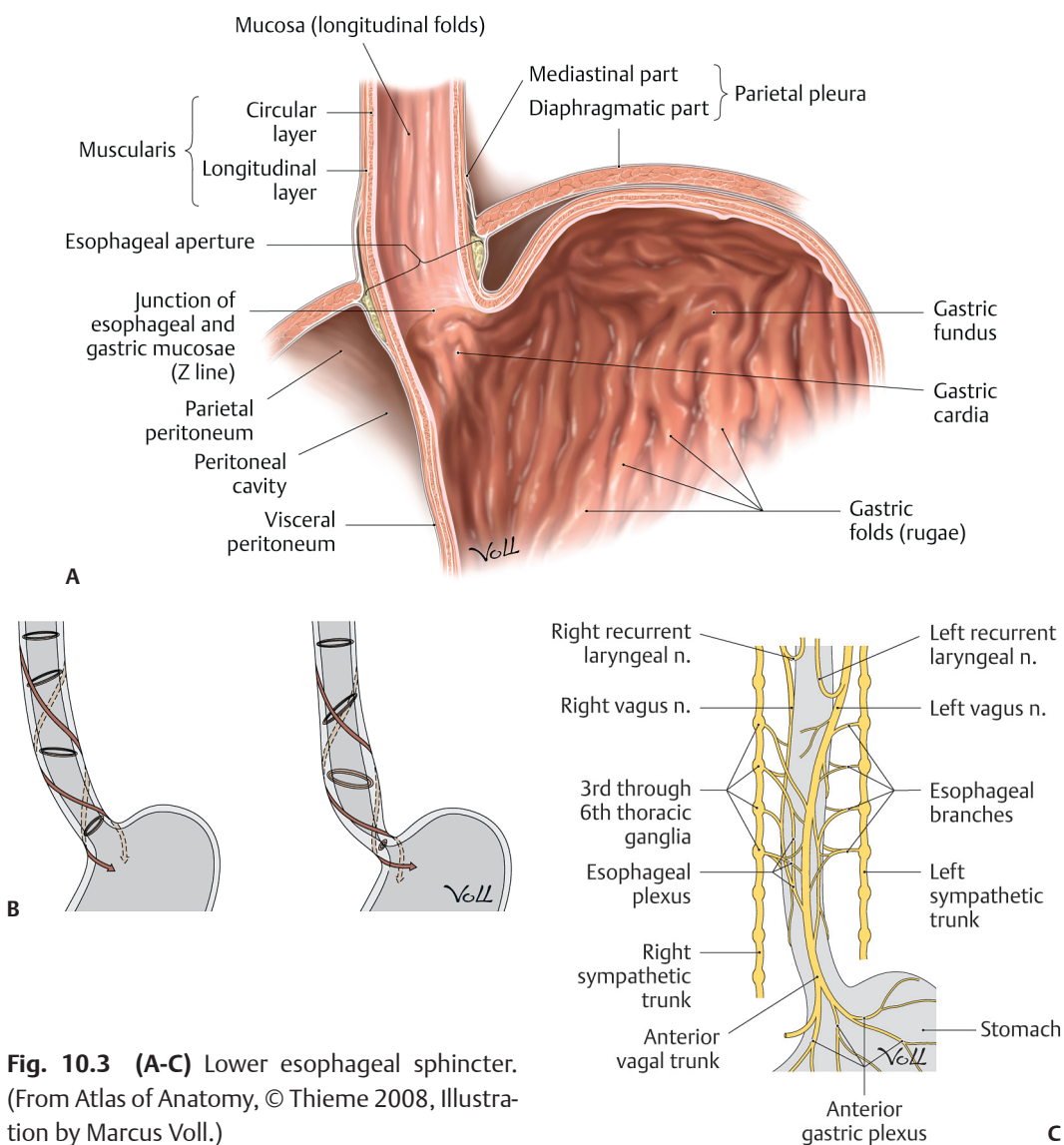


Fig. 10.3 (A-C) Lower esophageal sphincter. (From Atlas of Anatomy, © Thieme 2008, Illustration by Marcus Voll.)

An advantage of performing this procedure under general anesthesia is the opportunity to additionally carry out rigid cervical esophagoscopy to rule out causes of dysphagia other than CA.

Complications and Pitfalls

For the transcutaneous approach adequate rotation for injection may not be

achieved in all patients. This technique is moderately difficult, especially in older patients. Diffusion of the toxin to the posterior cricoarytenoid muscles can cause a bilateral vocal cord paresis. If severe enough, it can require a temporary tracheostomy. Special care should also be exercised in patients whose esophagram or manometry study shows retrograde peristaltic waves, as increased reflux and

regurgitation will likely occur if the cricopharyngeus muscle is weakened.

may develop chest discomfort after the procedure, and 10% may develop gastroesophageal reflux.¹⁵

■ Lower Esophageal Sphincter Technique

Endoscopic

This technique can be done with either rigid or flexible esophagoscopes in an outpatient setting. The position of the LES is identified by visualization of the Z-line and the typical narrow segment of the cardia region. Twenty units of BoNT are then injected into four quadrants (total of 80 U). No postinjection radiographic imaging is required. The patients can begin eating 2 hours after the procedure.

Complications and Pitfalls

The rate of serious complications is extremely low. Twenty percent of patients

Follow-Up

The injection may be repeated if symptoms return.

■ Conclusion

Botulinum neurotoxin injection into the various hyperfunctioning muscle groups of the hypopharynx and esophagus can be a safe and effective means of temporarily relieving the associated dysphagia symptoms. If the BoNT treatment proves effective, it can be repeated every 4 months, or as needed. Use of BoNT also plays a very important role as a diagnostic modality to identify patients who will benefit from surgical myotomy.



Video 16 Cricopharyngeus Muscle

These injections are given bilaterally into the cricopharyngeus muscle. A dose of 2.5 U/0.1 cc is given at two sites on each side of the pharynx. These injections should be given 1 cm below the bottom of the cricoid cartilage. The needle is advanced until activity is heard. If in the cricopharyngeus muscle, the activity should abate on swallowing.

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Palatal Myoclonus

Ajay E. Chitkara and Daniel Novakovic

Palatal myoclonus (PM) refers to the involuntary rhythmic muscular contraction of the soft palate. It was categorized as palatal tremor at the First International Congress of Movement Disorders in 1990, though the terms are often used interchangeably in the literature.¹ Palatal tremor (PT) is subclassified into symptomatic palatal tremor (SPT) and essential palatal tremor (EPT). SPT is typically one facet of a complement of symptoms involving the head, neck, and face. SPT is infrequently symptomatic at the level of the palate, and rarely requires medical treatment. EPT, however, generates a symptomatic ear clicking from the inappropriate palate contractions. The end-organ difference between SPT and EPT is thought to be the reason for the variance of symptoms: SPT is posited to involve the levator veli palatini (cranial nerves IX and X), whereas EPT is presumed to involve the tensor veli palatini (cranial nerve V) (**Fig. 11.1; Table 11.1**). Contraction of the tensor is associated

with the rapid opening of the eustachian tube, creating a sudden drop in tubal surface tension resulting in the audible snap, crack, or pop as often described² (**Fig. 11.2**). Palatal tremor may involve one or both sides of the soft palate, oscillating at a frequency of 0.5 to 300 Hz. The typical age for EPT is 25 years compared with 45 years for patients with SPT.³ Despite the subclassification of palatal tremor into SPT and EPT, there is evidence supporting a spectrum of palatal tremor disorders, as some patients do not clearly fit into one subclass or the other.¹

■ **Diagnosis**

Diagnosis of palatal myoclonus relies on the history and a neuro-otorhinolaryngologic evaluation. The most common complaint is the characteristic clicking tinnitus, which may be audible to the examiner. When the tremor is symp-

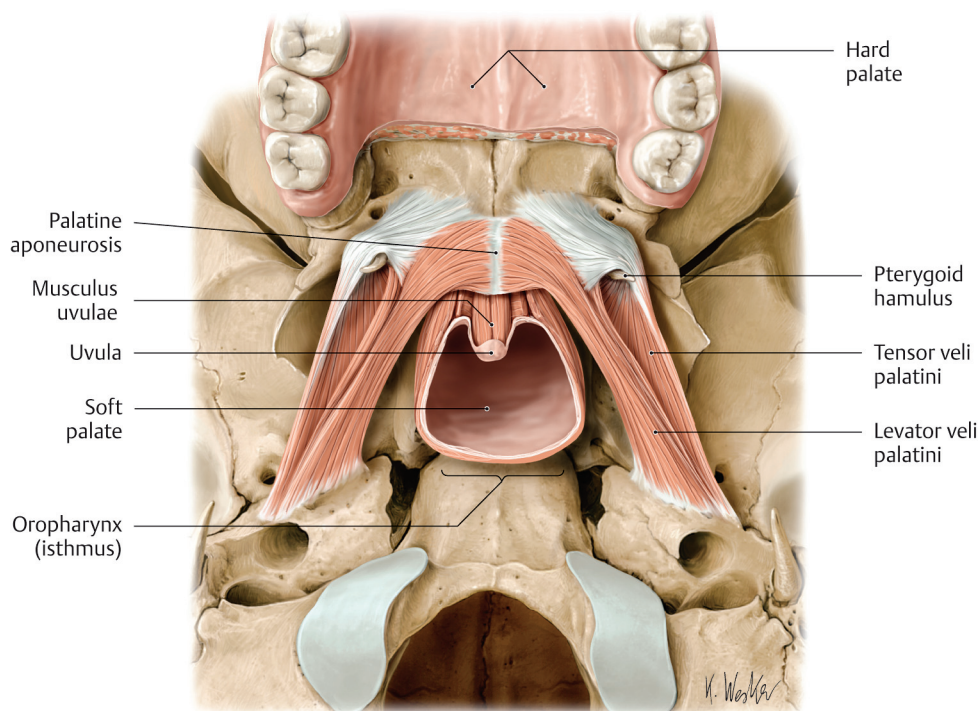


Fig. 11.1 Muscles of the soft palate. (From Atlas of Anatomy, © Thieme 2008, Illustration by Karl Wesker.)

tomatic (i.e., essential palatal tremor), imaging and laboratory evaluations are usually normal. Despite the paucity of diagnostic findings, neurologic assessment is often indicated to define or exclude any associated or underlying abnormality. Symptomatic palatal tremor is usually devoid of any palate-specific symptoms, though it is associated with other neurologic movement disorders of the head and neck. These associated movements may include the larynx, pharynx, face, or other structures controlled by the brainstem or cerebellum. SPT is often synchronous with the extrapalatal myoclonic structures.³ Symptomatic palatal tremor warrants a full neurologic evaluation.

Etiology of SPT may be identified as imaging changes in the inferior olive or dentato-olivary tract. SPT has been associated with numerous systemic metabolic, immunologic, infectious, and traumatic disorders (**Table 11.2**). There is no clear etiology of EPT, although there are rare reports of imaging abnormalities involving the inferior olive.⁴

■ Treatment

Treatment of palatal myoclonus with botulinum neurotoxin (BoNT) is based on the role of the tensor veli palatini as the source of the symptomatic clicking. Thus, despite the underlying subclassifi-

Table 11.1 Muscles of the Soft Palate

<i>Muscle</i>	<i>Origin</i>	<i>Insertion</i>	<i>Innervation</i>	<i>Action</i>
Tensor veli palatini	Medial pterygoid plate (scaphoid fossa); sphenoid bone (spine); cartilage of pharyngotympanic tube	Palatine aponeurosis	Medial pterygoid n. (cranial nerve V ₃ via otic ganglion)	Tightens soft palate; opens inlet to pharyngotympanic tube (during swallowing, yawning)
Levator veli palatini	Cartilage of pharyngotympanic tube; temporal bone (petrous part)			Raises soft palate to horizontal position
Musculus uvulae	Uvula (mucosa)	Palatine aponeurosis; posterior nasal spine	Accessory n. (cranial nerve XI, cranial part) via pharyngeal plexus	Shortens and raises uvula
Palatoglossus	Tongue (side)	Palatine aponeurosis	(vagus n., cranial nerve X)	Elevates tongue (posterior position); pulls soft palate onto tongue
Palatopharyngeus				Tightens soft palate; during swallowing pulls pharyngeal walls superiorly, anteriorly, and medially

(From Atlas of Anatomy, © Thieme 2008.)

cation of the palatal tremor, treatment should initially target the tensor when remediating the clicking tinnitus is the goal of therapy. In the United States, onabotulinumtoxinA is the most widely used formulation of BoNT/A. Typical treatment consists of one or two injection sites per side of the soft palate, placing 2.5 units (U) per injection site for an initial dose of 2.5 to 5 U per side. Reported dose ranges can vary from 2.5 to 15 U of BoNT/A per side of the pal-

ate.^{5–8} These injections are best performed under electromyographic guidance with a 27-gauge monopolar injection needle to maximize precision in locating the target muscle. The BoNT is diluted to 2.5 U per 0.1 mL of saline (4 mL saline per 100-U vial of onabotulinumtoxinA). Injections are typically performed in the ambulatory setting. Topical anesthesia may be applied to the pharynx. Under direct transoral visualization, the injection needle is placed

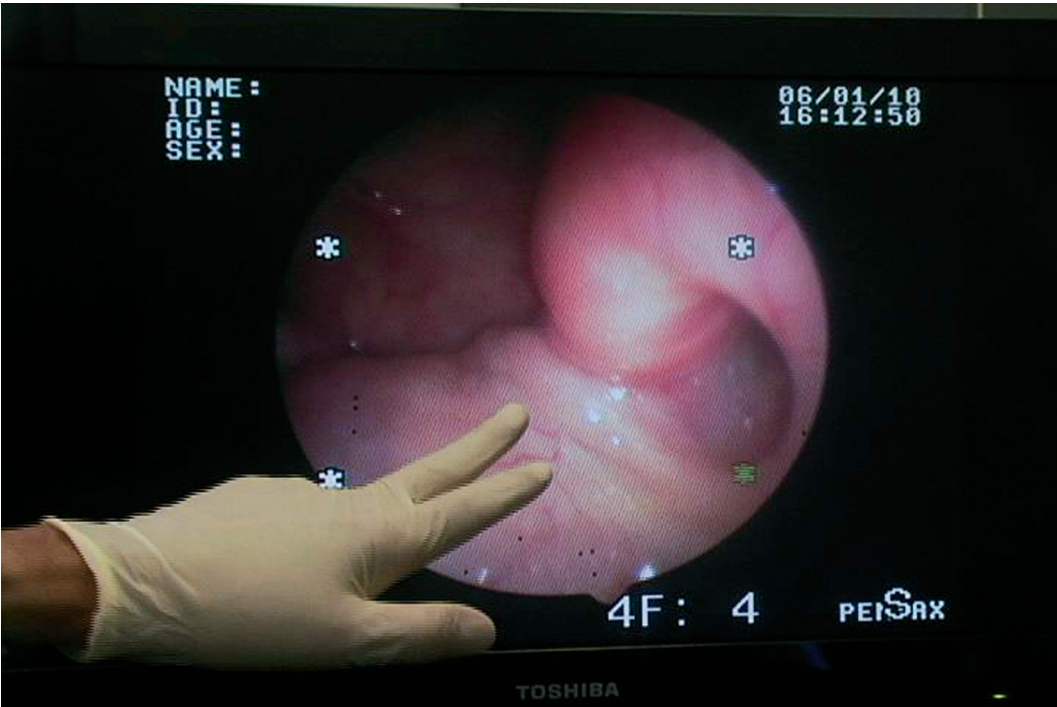


Fig. 11.2 Eustachian tube orifice.

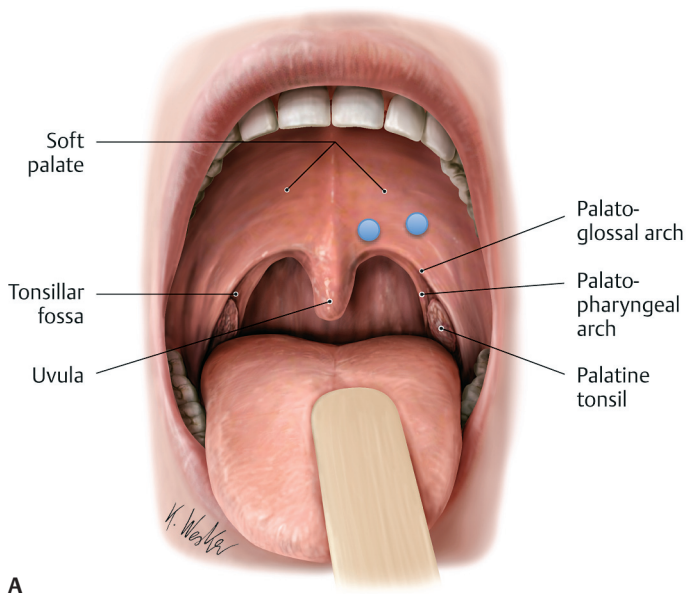
approximately 3 to 5 mm posterior to the posterior edge of the hard palate, in the lateral half of the affected side of the soft palate musculature (**Fig. 11.3**).

If treating a second site on the same side, then this second injection should be placed 3 to 5 mm posterior to the

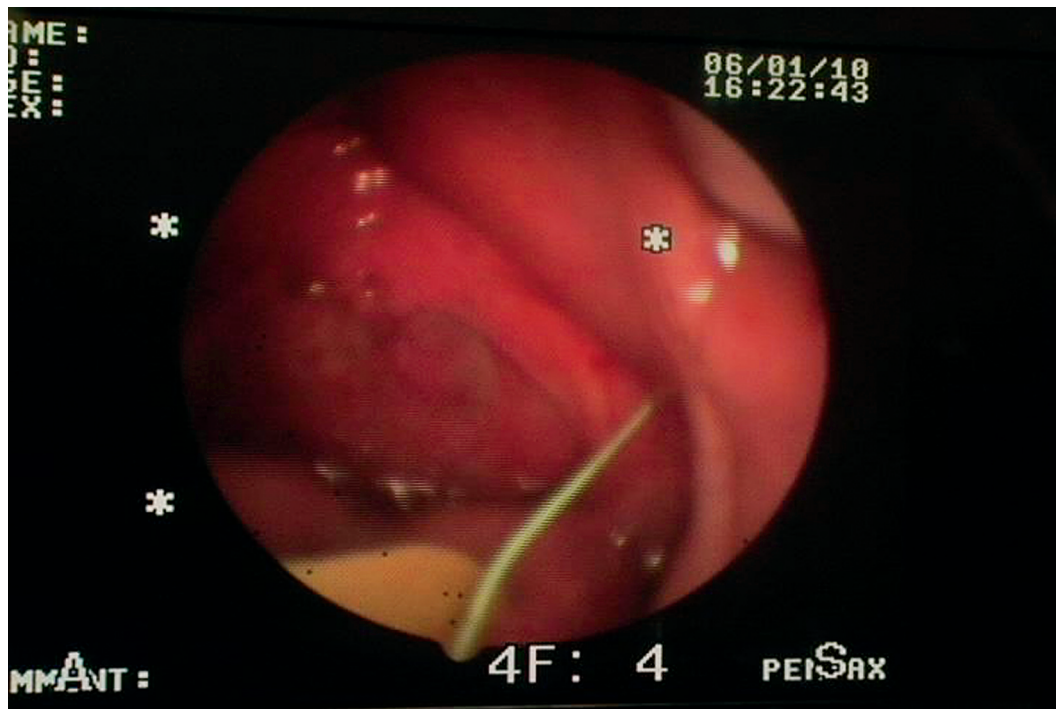
posterior edge of the hard palate adjacent to the base of the uvula in the medial half of the hemipalate. This places the toxin into the tensor veli palatini. Placement of the injection too far posterior or anterior in the soft palate may result in dysphagia due to denervation

Table 11.2 Causes of Symptomatic Palatal Tremor

Hereditary syndrome
Familial leukodystrophy
Neurodegenerative disorders
Ischemia
Trauma
Viral encephalitis
Malaria
Multiple sclerosis
Cerebrotendinous xanthomatosis
Behçet's disease
Krabbe's disease
Sclerosing leukoencephalopathy
Immunologic



A



B

Fig. 11.3 (A) Injection of palate. (From Atlas of Anatomy, © Thieme 2008, Illustration by Karl Wesker.) **(B)** Palate injection.

of the posterior or anterior fasciculus of the palatopharyngeus muscles, respectively, with limited improvement in the clicking tinnitus. The patient returns for follow-up 2 to 4 weeks after the initial injection, at which time the symptomatic benefit and any untoward effects can be assessed. A booster injection may be required at the follow-up if the patient is not realizing adequate benefit from the initial injection dose. The dose at follow-up, and at subsequent visits, should be titrated according to the patient's response to the prior injections. After the first one to three injection cycles, most patients can limit their follow-up to the injection visits only. At each visit, the treatment outcome is reviewed with the patient. When necessary, adjustments are made in the dosing and occasionally the location of injection sites to maximize symptom improvement and minimize the downside of the injections. Occasionally, injections into the tensor veli palatini do not adequately extinguish the tremor. Some clinicians have had success injecting the levator veli palatini or injecting the salpingopharyngeus muscle via an endoscopic endonasal approach.^{9,10}

Most patients require repeated injections at 3- to 6-month intervals. Though the duration of effect of the BoNT is approximately 4 months, some patients have reported resolution of symptoms after a single injection cycle. It is thought that some of these patients may have demonstrated a psychogenic variant of palatal myoclonus.^{11,12} Pharmacologic management of palatal myoclonus may be attempted, though it is rarely success-

ful as the sole treatment. In patients who are treated with systemic medication, BoNT injections may provide complementary benefit to the palatal myoclonus.

■ Complications and Pitfalls

Patients undergoing BoNT therapy are counseled regarding the general risks associated with use of the toxin. The typical dose range used for palatal myoclonus is a relatively low total systemic dose, and therefore it poses an extremely low risk of systemic side effects.

The majority of adverse outcomes relates to the local musculature involved in treating the soft palate. This can manifest as velopharyngeal insufficiency, which may result in dysphagia or dysarthria. The resultant hypernasal speech or nasopharyngeal regurgitation will peak within the first 2 weeks after injection and gradually subside thereafter.^{5,7,13} However, because these effects are dose related, they may persist in patients with profound sensitivity to the toxin, or in patients who were administered higher than usual doses.

The target muscle of these injections is the tensor veli palatini. One of the main functions of this muscle is opening of the eustachian tube and the subsequent equalization of middle ear pressure. By weakening the tensor, there is often resultant eustachian tube dysfunction. If these symptoms are severe, they may be treated with pneumatic equalization tube placement. Diffusion or injection of the toxin into the palato-

pharyngeus muscle could result in weakening of the upward and anterior elevation of the pharynx contributing to dysphagia. Theoretical complications of bleeding or infection at the injection sites have not been reported in the literature.

■ Conclusion

Palatal myoclonus is an uncommon movement disorder affecting the phar-

ynx. Medical management alone is rarely successful. The use of BoNT through localized injections into the tensor veli palatini can relieve the symptoms with minimal risk and relatively low side effects. The effective use of BoNT is predicated upon comprehensive understanding of the toxin by the administering physician and extensive counseling with the patient regarding the typical cyclical nature of therapy with the toxin, its desired effects, and the potential undesired effects.



Video 17 Palatal Myoclonus

With a transnasal endoscope in place, the irregular myoclonic jerks can be seen in the lateral aspect of soft palate and the palatopharyngeus muscle. The injection with EMG needle guidance is given transorally. A dose of 2.5 U/0.1 cc is given into the left side of the palate.

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Temporomandibular Disorders, Masseteric Hypertrophy, and Cosmetic Masseter Reduction

Joanna B. D'Elia and Andrew Blitzer

Temporomandibular disorder (TMD) is the most common cause of facial pain after toothache. Two forms exist, which can occur independently or simultaneously. The first is myogenous, or muscle related, and is the more common of the two types. The second is arthrogenous, or joint related.

Botulinum neurotoxin (BoNT) has been used successfully in the treatment of chronic pain syndromes of muscular origin and in various headache syndromes. In addition, BoNT has been proposed as an effective treatment for spastic conditions of the head and neck such as oromandibular dystonia and torticollis.¹ Consequently, clinicians have started using BoNT for treatment of TMD, bruxism, and masseteric hypertrophy with success. In 2001, Von Lindern et al²

treated seven patients for masseter and temporalis hypertrophy and noted a marked decrease in the size of the affected musculature with no relapse after a follow-up period of 25 months. In a second larger study, the sample size was increased to 90 patients, and patients were randomized to receive either BoNT or saline; 90% of the patients receiving botulinum had a decrease in their chronic facial pain.

Freund and Schwartz³ treated 46 patients with BoNT/A for TMD symptoms and assessed them at 2- and 8-week intervals for subjective pain, mean maximum voluntary contraction, interincisal oral opening, and tenderness to palpation. All patients demonstrated an improvement in all outcome measures except maximum voluntary contraction.

Maximum voluntary contraction was reported to decrease after 2 weeks but then revert to baseline levels at 8 weeks.

In an unpublished open label study by Bentsianov et al,⁴ the authors discovered a 70% response rate (defined as 50% reduction of severity and/or frequency of pain) when using BoNT injection into the masseter and temporalis muscles for TMD symptoms. Another study by Kurtoglu et al⁵ examined 24 patients who underwent either saline (placebo) or BoNT/A injection into the masseter and anterior temporal muscles. On days 14 and 28, electromyography (EMG) recordings were taken and each patient completed a subjective questionnaire, which revealed decreased muscle action potentials in 14 days and demonstrated improvement of pain and psychological status.⁵

Nixdorf et al⁶ reported in 2002 a randomized controlled trial of BoNT/A for chronic myogenous orofacial pain. This

study involved 15 women with pain of masticatory muscles and showed no statistically significant differences between control and placebo groups and a decrease in maximal interincisal opening. However, this study involved only a small sample size, and many patients dropped out due to the tight restriction on analgesics (acetaminophen only).

■ Anatomy

The temporomandibular joint is a synovial joint with articular surfaces on the condyle inferiorly, and articular tubercle and mandibular fossae of the squamous portion of the temporal bone superiorly. The articular surfaces are separated by an articular disk (or meniscus), which is a fibrocartilaginous structure providing a gliding surface for the condyle (**Fig. 12.1**).

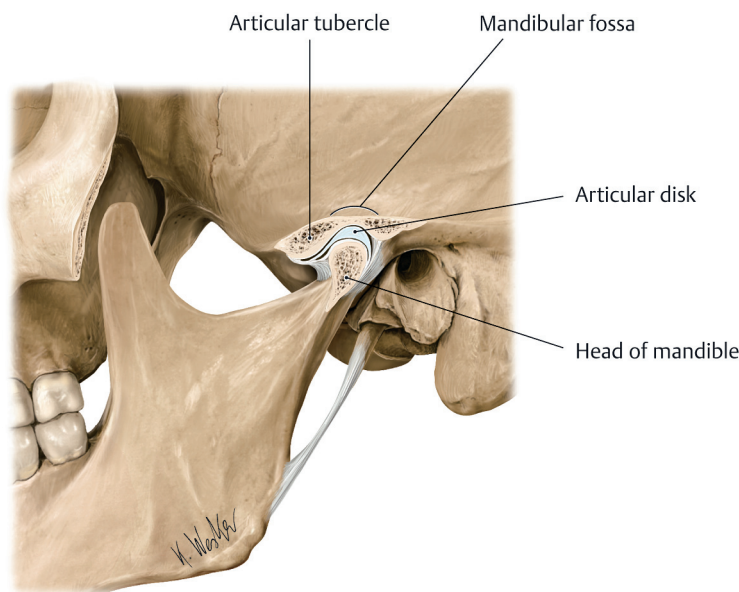


Fig. 12.1 Temporomandibular joint. (From Atlas of Anatomy, © Thieme 2008, Illustration by Karl Wesker.)

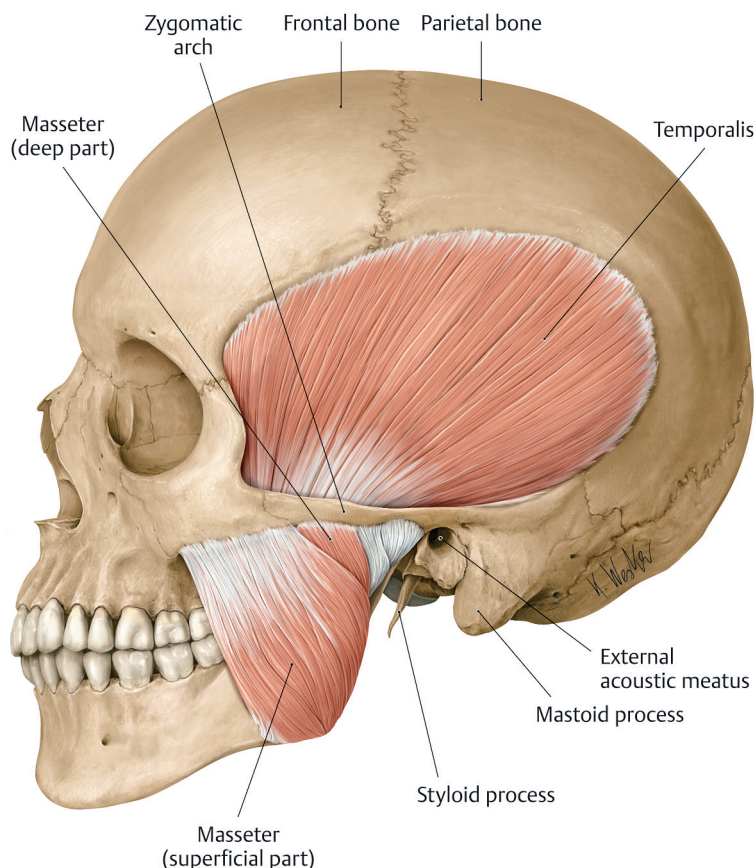


Fig. 12.2 Masseter muscle. (From Atlas of Anatomy, © Thieme 2008, Illustration by Karl Wesker.)

The adduction of the mandible (elevation or closing) is performed by the actions of the masseter (**Fig. 12.2**), temporalis (**Fig. 12.3**), and medial pterygoid (**Fig. 12.4**). The mandible is actively abducted (depressed or opened) by the lateral pterygoids (**Fig. 12.5**) and the supra- and infrahyoid musculature. Lateral excursion is allowed by actions of the contralateral pterygoids and masseter and the ipsilateral anterior portion of the temporalis muscles (**Tables 12.1** and **12.2**).

■ Patient Selection

Patients should be at least 18 years old and have had symptoms for at least 3 months that have been refractory to conventional treatments for at least 6 weeks. The following patients should not be considered for BoNT therapy: patients with proven arthrogenic TMD, those who have had prior surgery for TMD, and patients using medications that have an effect at the neuromuscular junction or who have another disorder

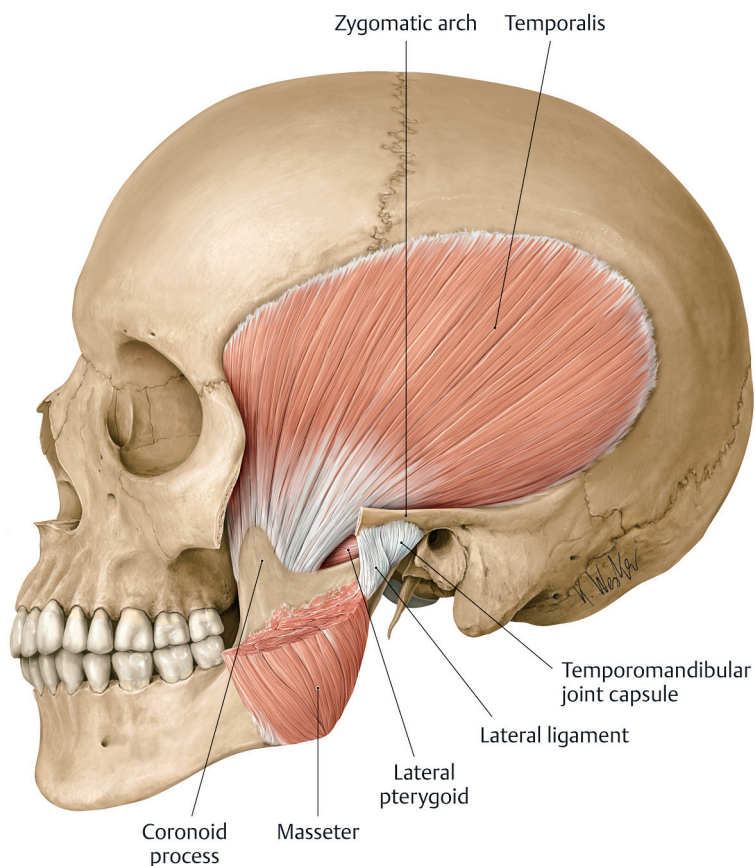


Fig. 12.3 Temporalis muscle. (From Atlas of Anatomy, © Thieme 2008, Illustration by Karl Wesker.)

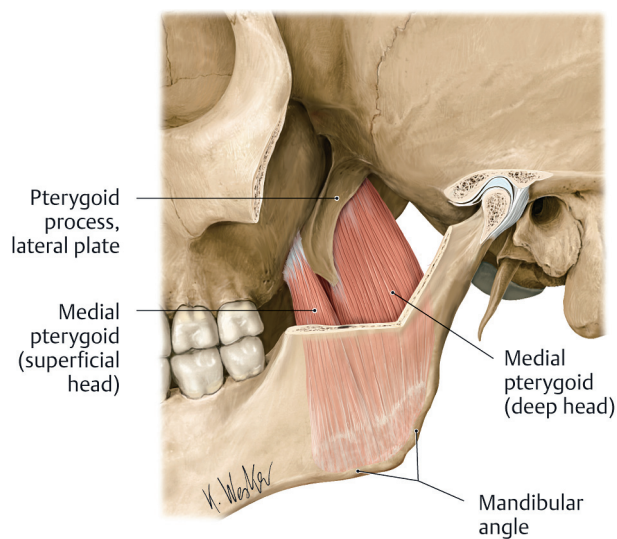


Fig. 12.4 Medial pterygoid. (From Atlas of Anatomy, © Thieme 2008, Illustration by Karl Wesker.)

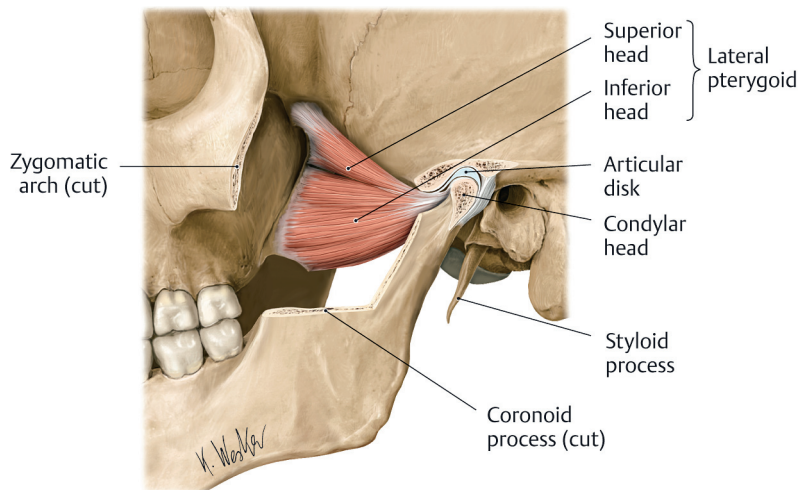


Fig. 12.5 Lateral pterygoid. (From Atlas of Anatomy, © Thieme 2008, Illustration by Karl Wesker.)

Table 12.1 Muscles of Mastication: Masseter and Temporalis

<i>Muscle</i>	<i>Origin</i>	<i>Insertion</i>	<i>Innervation</i>	<i>Action</i>
1. Masseter	Superficial part: zygomatic arch (anterior two thirds) Deep part: zygomatic arch (posterior one third)	Mandibular angle (masseteric tuberosity)	Mandibular n. (cranial nerve V ₃) via masseteric n.	Elevates (adducts) and protrudes mandible
2. Temporalis	Temporal fossa (inferior temporal line)	Coronoid process of mandible (apex and medial surface)	Mandibular n. (cranial nerve V ₃) via deep temporal nn.	<i>Vertical fibers:</i> elevate (adduct) mandible <i>Horizontal fibers:</i> retract (retrude) mandible <i>Unilateral:</i> lateral movement of mandible (chewing)

(From Atlas of Anatomy, © Thieme 2008.)

Table 12.2 Muscles of Mastication: Pterygoid Muscles

Muscle		Origin	Insertion	Innervation	Action
Lateral pterygoid	3. Superior head	Greater wing of sphenoid bone (infra-temporal crest)	Temporo-mandibular joint (articular disk)	Mandibular n. (cranial nerve V ₃) via lateral pterygoid n.	<i>Bilateral:</i> protrudes mandible (pulls articular disk forward)
	4. Inferior head	Lateral pterygoid plate (lateral surface)	Mandible (condylar process)		<i>Unilateral:</i> lateral movements of mandible (chewing)
Medial pterygoid	5. Superficial head	Maxilla (tuberosity)	Pterygoid tuberosity on medial surface of the mandibular angle	Mandibular n. (cranial nerve V ₃) via medial pterygoid n.	Elevates (adducts) mandible
	6. Deep head	Medial surface of lateral pterygoid plate and pterygoid fossa			

(From Atlas of Anatomy, © Thieme 2008.)

that interferes with neuromuscular function (e.g., myasthenia gravis).

Bentsianov et al⁴ suggest using a Visual Analogue Scale (VAS) score greater than or equal to 4 but less than or equal to 9 on an 11-point scale as an additional patient selection criterion.

■ History and Physical Examination

A comprehensive history and physical examination with a focus on the head and neck is mandatory. It is important to include a dental history and examination as well. It is particularly important to ascertain if there is a history of psychological issues, emotional stress, facial trauma, or poor dental care.

Symptoms associated with TMD are pain (generally periauricular), especially with chewing; headaches; clicking, popping, or snapping of the jaw; limited range of mandibular movement and locking episodes; changes in occlusion; masticatory difficulty; otalgia; and neck, shoulder, or back pain.

On physical examination, the physician should look for malocclusion, abnormal dental wear, missing teeth, and visible clenching or spasm of ipsilateral neck muscles. The temporomandibular joint should be palpated just below the zygomatic arch and 1 to 2 cm anterior to the tragus. Palpation should occur in both the open and closed positions. Determine the presence or absence of spasm, tenderness, and joint sound. Palpate the masseter, temporalis, ptery-

goids, and sternocleidomastoid muscles carefully.⁷

■ Laboratories and Imaging

Usually blood work is unnecessary unless systemic illness is suspected. In this case a complete blood count (CBC), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), and/or antinuclear antibody (ANA) may be helpful. If the diagnosis is unclear from the history and physical examination alone, or medical management has been unsuccessful, imaging may be considered.

Conventional radiography is usually sufficient and may show erosion, sclerosis, or remodeling. Computed tomography (CT) scan can explore both bony and soft tissue structures of the joint. Magnetic resonance imaging (MRI) may be considered if articular or meniscal pathology is suspected, if trauma has occurred, or if a surgical procedure is planned.

■ Pathophysiology

The underlying cause of myogenous TMD is muscular hyperactivity and dysfunction secondary to malocclusion, bruxism, hypermobility, or external stressors. Also, psychological factors may play a role.

Arthrogenous TMD is most commonly caused by disk displacement. It may also occur secondary to diseases such as degenerative disk disease, rheumatoid arthritis, ankylosis, dislocation infection, and neoplasia.⁴

■ Treatment Options

Conservative therapy options include patient education and self-care practices, adherence to a soft diet, physical therapy, occlusal splints, medication (non-steroidal antiinflammatories, muscle relaxants, tricyclic antidepressants), and biofeedback. Other alternatives include injection of BoNT as well as more invasive therapies such as arthrocentesis, arthroscopic surgery, and open surgery.

Eighty percent of patients may respond to conservative treatments. Surgery should be considered only if internal derangements, adhesions, fibrosis, or degenerative disk disease is present.⁴

■ Technique

A 27-gauge, hollow-bore, monopolar EMG electrode is placed into the muscle, which has been carefully palpated and identified prior to any procedure. The patient is first asked to activate the muscle (“bite down” in the case of the masseter) to verify correct placement of the needle. The intramuscular injection of the toxin is then initiated. The depth of injection approximates the belly of the muscle and should not be any deeper.

The required total dosage varies among patients, but we typically begin with a starting dose of 25 units (U) (100 U BoNT/A diluted with 2.0 mL of 0.9% sterile saline, resulting in a concentration of 5.0 U per 0.1 cc) to each masseter and temporalis muscle as symptoms dictate. This dose should be administered in five

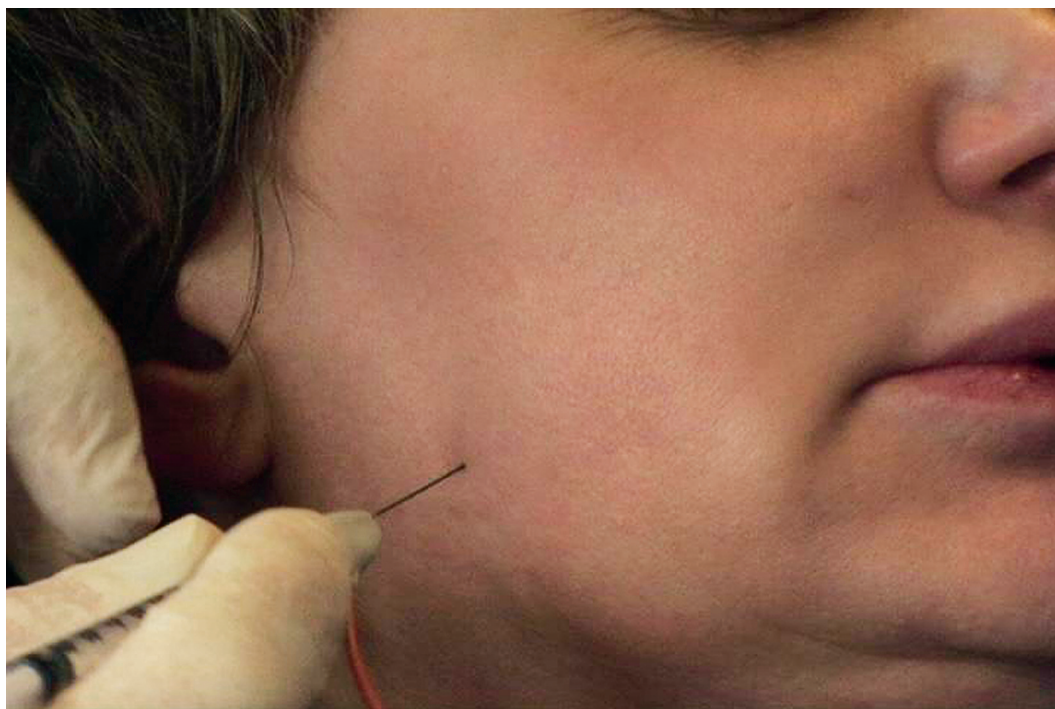


Fig. 12.6 Masseter muscle injection.

separate injections of 0.1 cc each of the aforementioned dilution, resulting in a total of 25 U in each individual muscle. The next scheduled dosage may be titrated up or down depending on the patient's response to the initial treatment.

The origin of the temporalis muscle is the floor of the temporal fossa, and it inserts into the medial surface of the coronoid process and anterior border of the ramus. The patient is asked to identify the points of maximal tenderness within this area, and the 25 U BoNT/A is dispersed into the muscle at five of these points. Special care should be taken to avoid the superficial temporal vessels, which can cause unnecessary and unsightly postinjection ecchymoses (**Fig. 12.6**).

The origin of the masseter muscle is the inferior border of the zygomatic arch. The insertion is onto the lateral surface of the ramus and coronoid process. The injections may be routed intraorally or transcutaneously, but the former is the more common technique. Again, a total of 25 U should be placed in each individual muscle, using five separate injections of 0.1 cc each (of 5 U/0.1 cc BoNT/A solution). Injection sites should be based on the patient's prior identification of the areas of maximal discomfort (**Fig. 12.7**).

Treatment of the lateral or external pterygoid is most beneficial for patients who have as their primary symptom teeth grinding or severe lateral excursions.



Fig. 12.7 Temporalis muscle injection.

sion. This injection should be given intraorally under EMG guidance. The lateral pterygoid plate is palpated, and the needle is placed between this plate and the coronoid process of the mandible. The needle should be oriented parallel to the length of the muscle. Once the needle is in position, the patient is asked to produce lateral excursions of the jaw to confirm proper placement. If it is in the proper location, bursts of motor endplate potentials will confirm this for the practitioner. The starting dose for each pterygoid muscle is typically 7.5 U per muscle (2.5 U/0.1 cc solution created by diluting 100 U BoNT/A with 4.0 mL of 0.9% sterile saline)⁴ (**Fig. 12.8**).

■ Complications and Pitfalls

The primary complications associated with injection of the masseter, temporalis, and lateral pterygoid are discussed in Chapter 5. The predominant issues involve weakening the muscles of mastication such that chewing becomes difficult. If this complication does occur, the patient should be reassured that chewing will return to baseline once the toxin wears off. Muscle wasting also may occur with repeated injections. Temporary pain or discomfort in the area of the injection is possible but is not a common complaint. Another uncommon complication is diffusion to the zygomaticus major muscle nearby, causing an adverse cos-



Fig. 12.8 Lateral pterygoid muscle injection.

metic effect and asymmetric smile. Generally speaking, complications are infrequent and the procedure is well tolerated by most patients.

■ Follow-Up

Patients may be evaluated at 2 weeks to assess the success of treatment. Patients should report any adverse effects. If pain or enlargement persists, the clinician

may elect to add additional toxin to the affected areas.

■ Conclusion

For carefully selected patients with TMD, BoNT is a safe and effective treatment option that may augment the efficacy of both traditional conservative measures and surgical interventions. Further research is required to establish specific selection criteria.



Video 18 Temporomandibular Disorders

(A) Masseter muscle injection: given with a hollow-bore EMG needle. Five sites are injected with 2.5 to 5 U/0.1 cc of Botox in each muscle. Once the needle is inserted, the patient is instructed to clench teeth to elicit activity. (B) Temporalis muscle injection: the areas of tenderness are elicited by palpation. In this patient, three areas in the anterior portion of the muscle are injected with 2.5 U/0.1 cc of Botox. (C) External pterygoid muscle injection: This muscle is best reached with EMG control with an intraoral approach. This allows the toxin to be accurately place along the length of the muscle. The patient is asked to move her jaw side-to-side to activate the muscle.

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Utilization of Botulinum Neurotoxin Therapy in the Laryngopharynx

***Craig H. Zalvan, Phillip C. Song,
Nwanmegha Young, and Andrew Blitzler***

For almost 20 years, botulinum neurotoxin (BoNT) has been the gold-standard treatment for spasmodic dysphonia. Since it was first publicized in mainstream society, the use of BoNT has grown at a staggering rate, with toxin being utilized in almost every field of medicine. Within the field of laryngology, the use of BoNT has also found a multitude of uses other than for spasmodic dysphonia. Almost any type of hyperkinetic or compensatory behavior found can be treated with the use of this toxin with a high degree of success, a low side-effect profile, and significant patient satisfaction. Toxin has been injected into the laryngopharynx for vocal tics, stuttering, vocal tremor, ventricular dysphonia, bilateral vocal fold paralysis, tracheoesophageal speech failure, as well as many other applications. By

using toxin, many of these symptoms are controlled more easily, often requiring less systemic medication. Also, toxin is used as an adjunct to other types of traditional therapy, such as voice therapy and swallowing therapy, and even to surgical interventions. Additionally, because of the physiologic effects of weakening muscle, the toxin can be used to “rebalance” the larynx. In cases of bilateral vocal fold paresis, selectively weakening the adductor muscles can provide for an adequate airway and help avoid a surgical intervention. Patients with vocal fold granulomas can benefit from toxin injection to help decrease the traumatic forces of the posterior glottis, thus decreasing the recurrence of granuloma and helping with resolution of persistent granulomas. In almost every situation of hyperfunction of the laryngeal

and extralaryngeal musculature, BoNT can be used to help ameliorate symptoms and provide significant, reproducible relief for patients.

As with most patients presenting with hyperfunctional disorders of the larynx, the primary diagnostic modality is laryngoscopy with or without stroboscopy. A detailed evaluation of the laryngopharyngeal structures demonstrates any abnormalities of function, including laryngeal closure, pharyngeal contraction, vocal fold motion, and laryngeal elevation. Additionally, anatomic abnormalities are visualized, indicating such findings as benign vocal fold mucosal disease, vocal fold granulomas, and excessive muscular tension. Typically, no further workup is necessary other than a thorough history and a physical examination of the head and neck.

The technique to perform electromyography (EMG)-guided injection of BoNT has been described extensively in previous chapters.

■ Bilateral Vocal Fold Paralysis

Bilateral vocal fold paralysis can be a devastating consequence of neck surgery, brainstem disease, or systemic disease that often leaves a patient with severe debilitation including shortness of breath and stridor with airway compromise. Patients often require airway intervention ranging from tracheotomy to simple posterior vocal fold cordectomy. Most laryngologists advocate waiting at least 1 year from the onset of the bilateral paralysis before performing a laryngeal de-

structive procedure to create an adequate airway to allow for laryngeal patency and removal of a tracheotomy tube. The problem arises when patients have bilateral vocal paresis with probable return of function. In these cases, patients are newly diagnosed with airway compromise and may be stable at rest or moderately symptomatic without distress. In this situation, a tracheotomy can possibly be avoided, removed early, or capped, by using BoNT injection into either a unilateral or bilateral thyroarytenoid and lateral cricoarytenoid (TA/LCA) muscle complex. By inhibiting the adductory function during reinnervation, the abductor muscles can contract unopposed, often leading to a larger airway caliber that allows for better airflow. In a recent study, 10 of 11 patients obtained substantial relief from airway obstruction after either bilateral or unilateral followed by bilateral BoNT injection into the TA/LCA complex.¹

Another group injected into the thyroarytenoid and interarytenoid muscles, yielding similar results of increased airway patency at rest and with activity. “Rebalancing” of the paralyzed vocal folds allowed for more abduction and hence a larger airway.² There has also been animal based research demonstrating the value of BoNT injection for bilateral vocal fold paralysis.³

Another use of BoNT in patients with bilateral vocal fold paralysis pertains to those with implantable laryngeal stimulators within the posterior cricoarytenoid muscle. By weakening the opposing adductory forces with chemical denervation, the airway patency was increased,

alleviating the symptoms of dyspnea. Thus by using electrical stimulation and chemical denervation, this group was able to decannulate patients with long-standing bilateral vocal fold paralysis.⁴

Typical treatment utilizing BoNT involves bilateral injections of the thyroarytenoid muscles utilizing the standard EMG-guided anterior neck approach; 2.5 units (U) of toxin is injected bilaterally as the initial dose. A second dose of 0.5 to 1 U can be injected 2 to 3 weeks after the initial dose if there has been little or no response. Typical side effects can range from no ill effects to severe breathiness and occasional coughing while drinking liquids. Gross aspiration is possible but has not occurred in our experience. Patients with severe airway compromise or progressive compromise despite BoNT injection are not good candidates for this type of medical intervention, and airway security is the primary concern.

■ Tracheoesophageal Speech Failure

Loss of voice after total laryngectomy is an unavoidable morbidity. However, with the widespread use of a tracheoesophageal puncture (TEP) and voice prosthesis, patients can develop and maintain the ability to communicate. A major disappointment occurs when that ability is lost again because of dysfunction of the prosthesis from fungal infection, dislodgement, and hyperfunction of the cricopharyngeus or pharyngoesophageal segment, preventing normal airflow through the TEP. In addition, some

laryngectomy patients initially fail an insufflation test of the pharyngoesophageal segment, demonstrating hyperfunction of this segment and likely poor TEP function.

The use of BoNT had repeatedly been shown to be an excellent adjunct in the treatment of these hyperfunctional disorders of the pharyngoesophageal segment. In cases where the diagnosis of failure of the TEP is uncertain, BoNT injection into the inferior constrictor and cricopharyngeal fibers can provide diagnostic information by either its success or failure. In addition, this can provide long-term treatment as well. By paralyzing the hyperfunctional muscle fibers, airflow through that segment is possible, allowing for diversion through the TEP and thus normal function. Typically the toxin is administered using EMG guidance and injecting transcutaneously through the neck; 50 U is the typical starting dose delivered bilaterally in equal doses. If there is no response, up to another 50 U can then be administered. The cricopharyngeus muscle is identified by finding baseline activity at rest, which diminishes with a swallow with prompt return of function after the swallow.^{5,6} Side effects are rare and may include some dysphagia from weakened constrictor muscles from toxin diffusion. Because of the alaryngeal state, there is no risk of aspiration or airway compromise.

■ Benign Vocal Fold Disease

Benign vocal fold disease such as vocal fold nodules, polyps, cysts, granulomas,

and hemorrhages all share a common etiologic factor: trauma. Chronic overuse of the voice, vocal abuse, acute phonatory trauma from coughing and yelling, and excessive Valsalva maneuver can all lead to thickening of the epithelium of the vocal folds, subepithelial fibrosis, and vocal hemorrhage. In many of these cases, voice therapy is the gold standard of treatment. Other cases require microsurgical intervention using a microflap technique of removal to optimize vocal outcome. However, often patients are reluctant to undergo surgery, and surgery does entail some inherent risk to long-term outcome. In certain circumstances, in patients with recurrent vocal fold benign disease, or dysphonia that persists despite voice therapy and surgery, BoNT can be used as an adjunct to temporarily weaken the adductory forces of the glottis to allow for healing or resolution of the benign vocal fold disease. By using this technique, there is no risk to the superficial lamina propria from surgical trauma. In addition, patients can continue undergoing voice therapy to help prevent recurrent lesions. Some patients can develop a temporary breathiness inherent in injecting the adductor muscles with BoNT. This tends to be short lived and is lessened by a decreased quantity of injected toxin if subsequent injections are deemed necessary.⁷ The typical starting dose is 1 U of toxin delivered by EMG-guided injection into the thyroarytenoid muscle. Side effects are typical for BoNT injection and include breathiness and possible aspiration. Mild breathiness for a few weeks is ideal, as this gives time for the mucosal pathol-

ogy to resolve. With ongoing voice therapy, these lesions can actually regress and often do not recur once behavioral changes have been made.

Although BoNT may be very successful for a variety of hyperkinetic laryngeal disorders, care must be taken to evaluate the larynx in a systematic and critical manner. We have used selective chemodenervation for a variety of conditions such as muscle tension dysphonia, laryngeal tremor, vocal cord dysfunction or paradoxical vocal fold motion, spastic dysarthria, arytenoids rebalancing, idiopathic chronic cough, and contact granulomas, and results can be variable. The following potential problems may occur with selective laryngeal chemodenervation using BoNT:

1. The specificity of injections may be inadequate due to inherent difficulties with site localization and diffusion of BoNT to adjacent muscles.
2. Diagnostic criteria and our ability to determine what is wrong are inadequate. Clinical examination and visualization during phonation are a rough guide to laryngeal activity. Visualization of the larynx with the endoscope allows a single angle of view that limits evaluation of inferior and deeper structures. In the case of muscle tension dysphonia and vocal hyperfunction, the true vocal folds are often obscured by the function of the supraglottic structures. Other tools such as laryngeal EMG (LEMG) may be a more sensitive instrument; however, in its current state, LEMG is still a rough tool.

3. A variety of dysfunction produces the same clinical appearance. For instance, muscle tension dysphonia can be the end result of hyperfunction of certain laryngeal muscle groups, hypofunction of others, paresis, poor coordination, inadequate or disruptive sensory feedback, or anatomic pathology.
4. A well-defined management algorithm incorporating selective chemodenervation for these conditions does not exist. Individual practitioners are using BoNT without a clear constructive clinical model, resulting in a wide range of injection techniques and therapies. Instead of treating botulinum injections like a surgical tool, it is perceived as a medication with a specific pharmacologic action. BoNT should be viewed as an instrument with properties of cutting or severing a nerve. Hence, use of this “chemical knife” correctly requires an individualized plan of care and treatment.

■ Muscle Tension Dysphonia

The success of BoNT for treating primary muscle tension dysphonia (noncompensatory) is based on proper and critical evaluation of larynx function to identify laryngeal pathology as well as analysis of laryngeal behavior to distinguish between compensatory and primary hyperfunction. Coordination with a trusted and experienced voice therapist is very important. BoNT injections are considered for those patients with severe symp-

toms who have failed voice therapy. Ongoing voice therapy is necessary because the BoNT injections are temporary, and long-lasting improvement depends on functional changes in laryngeal behavior. The injections can be considered a temporary chemical “splint” that forces reduction in hyperfunctional behavior. However, until the patient understands and can control the behavior, the voice symptoms are likely to return. In fact, there may be a danger in exacerbating the symptoms if the behavior is exaggerated or new dysfunctional compensatory strategies develop. An additional usage of botulinum would be to unload the larynx to reveal laryngeal pathology that was previously not seen secondary to the hyperfunction.

Kendall and Leonard⁸ reported a series of seven patients with ventricular dysphonia treated with BoNT injections, resulting in substantial relief in five. The authors administered the injections onto the false vocal folds/aryepiglottic fold junction, which was followed by traditional voice therapy. In our experience, the area and dose of injection can vary based on the clinical evaluation of the larynx and determination of the hyperfunctional muscles.

■ Evaluation

It is critical to ascertain which laryngeal muscles are dysfunctional. There are several ways to categorize types of laryngeal muscle tension dysphonia. Supraglottic manifestations of hyperfunction include ventricular hyperfunction, which is over-

closure of the false vocal folds over the true ones; anterior posterior compression, which refers to overclosure secondary to the epiglottis and arytenoid complex narrowing; and sphincteric closure, in which both dimensions are incorporated, closing off the larynx. Muscle tension may also be the product of excessive tension of the vocal folds without significant supraglottic activity. There may be overrotation of the LCA, creating a posterior glottic gap and excessive protrusion of the vocalis process. There may also be excessive cricothyroid muscle motion leading to a lengthened and tight vocal fold. Additionally, hyperfunction of the transverse arytenoid muscle could result with a scissoring action of the posterior glottis.

■ Botulinum Therapy

For lateral hyperfunction or hyperfunction causing predominantly lateral hyperfunction, excessive length and tension of the true vocal folds, the TA and LCA are the most commonly addressed groups of muscles. LCA hyperfunction can be manifested by overrotation of the posterior glottis, forming a prominence of the vocalis process or a Y-shaped posterior glottal gap. If there is determined to be significant hyperfunction of the cricothyroid muscle, as manifested by increased pitch, a lengthened vocal fold, and tension/pain in the cricothyroid visor, cricothyroid injections should be tried. Interarytenoid injections can also be given in cases where overactive transverse arytenoids muscles are suspected.

Botulinum neurotoxin injections can be performed on the larynx via transcutaneous EMG-guided methods. A good starting dose for treating muscle tension dysphonia is about 2.5 to 5.0 U per side. The dose is higher than our standard initial dose for spasmodic dysphonia. The patient should have some breathiness and loss of projection after the injection. Possible side effects include dysphagia (typically coughing and choking on thin liquids),odynophagia, local injection site reactions such as bruising and bleeding, and a very rare chance of regional diffusion of the Botox into other sites.

■ Puberophonia

Puberophonia is a hyperfunctional vocal disorder that afflicts primarily teenage boys. The underlying condition is the retention of the prepubescent voice after puberty. This may be secondary to a “nonacceptance” of the new, mature, male voice or a regression back to prepubescent vocal patterns, resulting in a high-pitched, feminized, or androgenous voice pattern. As with all laryngeal applications for BoNT, care must be taken to identify and correct the hyperfunctional muscle groups.

The first line of treatment is always with an experienced voice pathologist who has expertise in the treatment of puberophonia. BoNT treatment may be indicated for patients with puberophonia who have failed voice therapy. Psychiatric evaluation to identify and treat emotional or cognitive obstacles to the

acceptance of the mature voice may be necessary prior to the procedure, especially in cases of regression and in older patients. For teenagers, the main problem may be physiologic adjustment difficulties during the transitional stages of laryngeal development.

The evaluation of puberophonia is similar to that of muscle tension dysphonia: identify the laryngeal muscle groups that are dysfunctional. Typically, the voice is high-pitched and strained. The cricothyroid and strap muscles are hyperfunctional with elevated tension along the vocal folds and a larynx that is in a “high” position. Palpation of the cricothyroid visor and the thyrohyoid space can elucidate these muscles. The laryngoscopy and stroboscopy should reflect the hyperfunctional behavior and be clear of other laryngeal disease. Ongoing voice therapy is important to help maintain the homeostasis.

In our experience, transcutaneous EMG-guided BoNT directed at the cricothyroid muscle and at the TA/LCA complex is generally the most successful treatment. The cricothyroid muscles can be identified with the EMG needle inserted lateral to the cricothyroid space, with the needle directed superficial to the cricoid lamina toward the lateral thyroid lamina. The starting dose is 5.0 mouse units per side. The patient is directed to begin phonation at the lowest pitch and perform a pitch glide into falsetto. With puberophonia, the EMG discharge is typically at the onset of phonation because the cricothyroid muscle is discharged even at the lower pitch range. The TA/LCA complex is treated with 2.5

to 5.0 mouse units, as is typical for other muscle tension disorders.

■ Tourette’s Syndrome and Laryngeal Tics

Tourette’s syndrome and laryngeal tics are neuropsychiatric disorders of uncontrollable motor and phonic impulses. For simple motor tics, there does seem to be an improvement in the frequency and premonitory or urge symptoms associated with the motor spasms. Manifestations of Tourette’s syndrome tend to be complex motor behaviors, and laryngeal Botox may be beneficial in reducing the loudness and volume of the vocalizations as well as in decreasing the frequency. The phonic tics may be short, brief involuntary movements or vocalizations. They are repetitive, but not regular or rhythmic in nature. The vocalizations can be simple (sniff, bark, throat clearing, or cough) or complex (echolalia, palilalia, and coprolalia). There is a significant association with psychiatric disorders such as attention deficit hyperactivity disorder, obsessive-compulsive disorder, and autism.

There has been one randomized prospective trial on the efficacy of BoNT for simple motor tics in the head and neck.⁹ In this study of 18 patients using BoNT in a variety of sites in the head and neck, the authors demonstrated an average reduction of 37% in tic frequency based on videotaped assessment as compared with saline injection.

Botulinum neurotoxin is considered an adjuvant symptomatic treatment. Pri-

mary pharmacologic treatment for Tourette's syndrome is based on functional disability. Treatment can range from simple observation and treatment of comorbid psychiatric conditions, to neuroleptic agents, primarily dopamine receptor blockers. Clonidine, guanfacine, clonazepam, and baclofen have been used for tic suppression with variable success. BoNT to the larynx can be useful for reduction and suppression in the volume and frequency of the involuntary vocalizations.

To reduce loudness and volume, BoNT is injected into the TA/LCA complex via transcutaneous EMG-guided method. The starting dose is usually 2.5 U per side and is higher than that used for spasmodic dysphonia. A weak, breathy, and asthenic voice is considered a natural part of the therapy.

■ Vocalis Process Granulomas

Laryngeal granulomas are abnormal rests of hypertrophic tissue composed of fibroblasts that arise in the posterior aspects of the vocal folds. These lesions are traumatic and inflammatory in nature, with a high degree of association with vocal hyperfunction and laryngopharyngeal reflux. The clinical behavior of these lesions ranges from indolent to aggressive, and symptoms are usually related to size. Small granulomas may be asymptomatic, whereas larger granulomas can result in dysphonia, dysphagia, and airway obstruction. Although contact granulomas that arise after intubation or trauma (postintubation granu-

lomas) often disappear with observation or treatment with antireflux therapy, idiopathic granulomas can be very difficult to manage. Idiopathic granulomas have a high rate of recurrence after removal, and surgery alone is not considered an effective means of treatment. These lesions are primarily managed medically, with voice rest, voice therapy, and antireflux therapy. BoNT can be used as a chemical splint to reduce trauma in the posterior vocal folds if initial management has failed.

The utility of BoNT injections in the larynx for vocalis process granulomas depends on the clinical evaluation of the etiology of the disease and the degree of laryngeal hyperfunction. Damrose and Damrose¹⁰ reported their experiences using laryngeal BoNT injection for refractory laryngeal granulomas in seven patients. They reported success in all seven of the treated patients using doses ranging from 10 to 25 U divided into both vocal folds. In our experience, BoNT injections have a high rate of initial success; however, long-term success often requires continued acid suppression therapy and changes in vocal behavior.

Botulinum neurotoxin injections in the presence of compensatory hyperfunction for glottal incompetence, such as that associated with sulcus vocalis, loss of superficial lamina propria, or presbylarynges, are more likely to fail, even with adequate voice therapy. In these cases, the posterior glottis undergoes excessive trauma in order for the patient to maintain a functional voice. Vocal fold augmentation to address the underlying glottal insufficiency may be

used in these cases to reduce posterior glottal striking forces.

The Botox delivered for the treatment of laryngeal granulomas undergoes similar evaluation as for primary muscle tension dysphonia. The most common injection sites are the TA/LCA complex and the interarytenoid muscles. The TA/LCA complex is treated with 2.5 to 5.0 mouse units, as is typical for other muscle tension disorders. In our hands, the interarytenoid injection is generally administered under direct visualization and a transcutaneous approach either superiorly through the thyrohyoid membrane or inferiorly through the cricothyroid membrane. The needle is seen traversing the glottic airspace and the injection is given in the interarytenoid region. Care must be taken not to insert the needle too deep, or it may infiltrate into the posterior cricoarytenoid (PCA). The TA/LCA injections may also be performed visually through the same approach.

■ Arytenoid Rebalancing

Arytenoid rebalancing with BoNT for the treatment of arytenoid dislocation has been described sporadically in the literature.¹¹ Arytenoid dislocation is often difficult to diagnose as the position of the arytenoid can be quite variable. Typically, anterior arytenoid dislocation produces a lax, bowed vocal fold with a medialized and anterior displacement of the arytenoid body. The anterior dislocation lowers the vocalis process, pro-

ducing a vertical mismatch that adds to the degree of glottal incompetence. This position is also common in the paralyzed vocal fold. There may be a line of demarcation at the junction of the cricoid and arytenoids in cases of complete dislocation. The posterior arytenoid dislocation results in a posterior and laterally positioned arytenoid with a taut vocal fold. In either case, the arytenoid is immobile and glottic incompetence is common. Evidence of supraglottic contraction may help in differentiating between dislocation and paralysis. The diagnosis usually requires manual palpation or the arytenoids, radiographic evidence of the arytenoid dislocation, and/or laryngeal EMG. Operative treatment to relocate the arytenoid by closed reduction is the most common practice. This is often attempted during direct laryngoscopy by pushing the arytenoids back over the cricoid ledge. However, surgical success producing arytenoid mobility and reestablishing glottic competence is rare. BoNT has been advocated as an adjuvant treatment to rebalance the arytenoid to guide it to a more functional position.

In an anteriorly displaced arytenoid, the posterior cricoarytenoid muscle is often torn or excessively lax because of the traumatic stretch injury. The treatment rationale is to rebalance the arytenoids on top of the cricoid ledge by weakening the adductor groups. The common targets are the interarytenoid muscles and the TA/LCA complex. This would produce a relative strengthening of the abductor (the PCA), resulting in a

more posterior arytenoid position. This can be performed during the surgical relocation attempt in the operating room or afterward in the office. For a posterior dislocation, the BoNT can be delivered to the PCA muscle with EMG guidance, thereby rebalancing toward the adductor muscle groups and moving the arytenoid anteriorly.

■ Chronic Idiopathic Cough

Botulinum neurotoxin therapy has been used for the treatment of unexplained chronic cough syndromes with variable success. Cough is a very common problem in the primary care setting and may be the result of inflammation (acid, allergy, and asthma), irritation (chemical), mechanical trauma (chronic throat clearing), anatomic factors (glottic stenosis, neoplasm, and vocal fold paralysis), or neurogenic inflammation along the respiratory tract. There are many idiopathic or poorly understood chronic cough disorders described that share overlapping features; these disorders include neurogenic cough, irritable larynx syndrome, psychogenic cough, and unexplained chronic cough. BoNT injection may be considered when other diagnostic and treatment options have been exhausted and the larynx is believed to be the source of the cough, usually because of concomitant laryngeal dysfunction (laryngospasm, dysphonia, or throat discomfort).

There are several hypotheses of how Botox may be beneficial in chronic cough.

In a neurogenic model of cough, there are numerous afferents carried via the sensory components of the vagus nerve that may become dysfunctional and sensitized, leading to a hyperexcitable state. The BoNT may block the release of specific neuropeptides that are responsible for stimulating a pathogenic peripheral sensitization cycle. Alternatively, the Botox may also act simply as a “chemical splint” to help stop habituated behavior, reduce mechanical trauma elicited through vocal hyperfunction, and reestablish laryngeal homeostasis.

To date, there have been only small case series describing the use of BoNT in chronic cough. Sipp et al¹² in 2007 described three children with a debilitating habitual cough treated with BoNT A with good success. Chu et al¹³ in 2010 described significant relief of cough with complete resolution in four patients after a series of injection (median of seven treatments) for about 2 years. In our experience, the use of BoNT for chronic cough has yielded more variable results. The BoNT may weaken the strength of the cough and decrease the traction and friction on the larynx, leading to a gradual decrease in traumatic inflammation. However, conversely, the patient may also experience increased aspiration and increased mucus, which may cause increased anxiety and provoke more cough and throat clearing. Concurrent pharmacologic treatment with antitussives is continued. The doses begin at about 5.0 U and continue for several treatment cycles at 2- to 3-month intervals.

■ Conclusion

Botulinum neurotoxin therapy is an extremely useful and versatile tool in the laryngologist's armamentarium. By chemically denervating the various laryngeal muscles, one is able to effectively diagnose and treat a number of disorders of the laryngopharynx. Most cases of dysphonia or dysphagia from a laryngeal cause are secondary to hyperfunctional behavior. Used as a "chemical knife," BoNT can allow for selective denervation of these hyperfunctional muscles, resulting in mitigation of symptoms and control of muscle spasm.

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■ S E C T I O N I I I ■

Pain Syndromes

14

Migraine

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Headaches are one of the most common patient complaints presented to physicians in the United States and a major cause of disability worldwide. Nearly 27.9 million of Americans suffer from moderate to severe migraine headaches, accounting for nearly 10 million physician visits annually.^{1,2} The debilitating nature of these disorders can result in significant loss of productivity, reduced social engagement, and poorer quality of life. Other associated neuropsychiatric conditions such as depression and anxiety complicate the morbidity. The socioeconomic burden can be measured in the billions of dollars incurred both direct (health care utilization) and indirect costs attributable to disability. Although the overwhelming majority of headache disorders are benign in nature, the fear of a more significant pathology (e.g., brain tumor or aneurysm) impacts both patients and physicians.

Not surprisingly, physicians, particularly those who are unfamiliar with headache management, request extensive and often unnecessary diagnostic examinations in search of organic pathology, adding to health care costs.

Management of migraine headache continues to evolve as many of the traditional therapeutics have failed to effectively treat the disorder. Compliance with prophylactic and abortive medications remains low because of inadequate efficacy and intolerable adverse effects. There exists a great demand for long-acting acute and prophylactic therapies that are effective, well tolerated, and devoid of significant systemic toxicities. Interest in the use of botulinum neurotoxin (BoNT) injection as an alternative therapy for migraine headache has gained popularity, and in 2010 BoNT/A was approved by the Food and Drug Administration (FDA) for the prophylactic

treatment of chronic migraine. Although the basic pharmacologic activity of the BoNT molecule is fairly well understood, the mechanism of action in headache prevention remains unclear. This chapter discusses the pharmacologic activity, proposed mechanisms of action, safety, and dosing of BoNT therapy for migraine headache.

■ Background and Classification

Cephalalgia, or headache, has plagued human beings since the beginning of time. The earliest available reference to a migraine-type headache was recorded among the Sumerian poems ca. 3000 BC, which described an individual as being “sick-headed.”³ The first reports of a patient describing altered visual perceptions, or aura, came from Hippocrates. During the second century AD, Aretaeus of Cappadocia delineated the symptom structure of what is commonly referred to as migraine with aura.⁴ More recently, scientific theories to explain the pathophysiology of migraine headaches have emerged. Liveing is credited with the origination of the *neural theory*, purporting that certain “disturbances” within the autonomic nervous system may account for the triggering and sustenance of the headache. Dey subsequently described the phenomenon of cyclical pituitary compression of the trigeminal nerve.³ In the 20th century, Harold Wolff, through experimental evidence, described a phenomenon of episodic extracranial vascular dilatation and constriction. His insights ultimately contrib-

uted to the formulation of the *vasogenic theory* of migraine.³

The word *headache* is used variously as a descriptive term, a symptom, and a disorder. The need for a formal headache classification schema arose to facilitate the diagnostic evaluation, communication and development of effective therapeutic modalities. The International Headache Society (IHS) published a classification system in 1988, the International Classification for Headache Disorders (ICHD-1), which categorized the major headache types, and distinguished primary from secondary headache disorders.⁵ Revised in 2003, the ICHD-2 defined a primary headache disorder as one for which no identifiable structural or organic cause is known (e.g., migraine and tension headaches). A secondary headache disorder required a known structural or systemic etiology as the cause of the headache symptom.⁶ Although the ICHD classification system has undergone much scrutiny, it nevertheless provides a basic structure upon which to initiate a rational approach to headache management.

The spectrum of migraine headache disorders has been coded by the IHS into six accepted subtypes, with notable subforms (**Table 14.1**). Migraine can be classified into two major subtypes, namely, with or without aura. Migraine without aura is the most prevalent migraine subtype, and may involve a higher frequency of attacks and greater disability than migraine with aura. The majority of common migraine headache patterns are considered episodic, to differentiate from the complicated subform of chronic

Table 14.1 Classification of Migraine Headache Disorders

- 1.1 Migraine without aura
- 1.2 Migraine with aura
 - 1.2.1 Typical aura with migraine headache
 - 1.2.2 Typical aura with non-migraine headache
 - 1.2.3 Typical aura without headache
 - 1.2.4 Familial hemiplegic migraine (FHM)
 - 1.2.5 Sporadic hemiplegic migraine
 - 1.2.6 Basilar type migraine
- 1.3 Childhood periodic syndromes that are commonly precursors of migraine
 - 1.3.1 Cyclical vomiting
 - 1.3.2 Abdominal migraine
 - 1.3.3 Benign paroxysmal vertigo of childhood
- 1.4 Retinal migraine
- 1.5 Complications of migraine
 - 1.5.1 Chronic migraine
 - 1.5.2 Status migrainosus
 - 1.5.3 Persistent aura without infarction
 - 1.5.4 Migrainous infarction
 - 1.5.5 Migraine-triggered seizure
- 1.6 Probable migraine
 - 1.6.1 Probable migraine without aura
 - 1.6.2 Probable migraine with aura
 - 1.6.3 Probable chronic migraine

(Adapted from the International Classification of Headache Disorders–II, International Headache Society, 2003. Reprinted by permission.)

migraine (classification code 1.5.1). The diagnosis of chronic migraine requires that the diagnostic criteria for migraine are met, with at least 15 or more headache days per month, for at least 3 months, in the absence of medication overuse.

■ Migraine Symptomatology

Headaches account for 1 to 2% of all emergency room visits, with migraine making up nearly 40% of headache-related visits.⁷ Nearly 18% of women and 6% of men are affected in the United States; however, these estimates may underreport the true incidence of disease as many patients go undiagnosed.

The disorder most commonly affects individuals between the ages of 25 and 55.⁸ Migraine is among the leading causes for missed days at work. Lost productivity at work or school, decreased quality of life, and familial and social dysfunction increase the risk of affective disorders among these patients.^{9,10}

Migraine is a paroxysmal headache disorder, with periods of relative quiescence between acute headache episodes. The International Headache Society put forth the criteria for diagnosis of migraine without aura (**Table 14.2**). Headaches typically manifest with moderate to severe throbbing head pain lasting hours to days, in a hemicranial, fronto-temporal distribution; however, bilateral and posterior cervical pain can occur.

Table 14.2 Criteria for Diagnosis of Migraine Without Aura

- A. At least five attacks fulfilling criteria B to D
- B. Headache attacks lasting 4 to 72 hours
- C. At least two of the following characteristics:
 - 1. Unilateral location
 - 2. Pulsating quality
 - 3. Moderate or severe pain intensity
 - 4. Aggravated by or causing avoidance of regular physical activity
- D. At least one of the following during headache:
 - 1. Nausea and or vomiting
 - 2. Photophobia and or phonophobia
- E. Not attributed to another disorder

(Adapted from the International Classification of Headache Disorders–II, International Headache Society, 2003. Reprinted by permission.)

Associated symptoms may include nausea, vomiting, anorexia, malaise, photo- or phonophobia, and blurred vision. Peculiar, transient neurosensory perceptions prior to or concomitant with the pain phase occur in migraine with aura. Headaches have been associated with intake of certain foods (meats and cheeses [high nitrites], nuts, chocolate), alcohol ingestion, caffeine withdrawal, menstruation, bright lights, and exercise. Patients often seek a dark, quiet environment for symptom relief.

■ Migraine Pathophysiology

The pathophysiology of migraine headache is not completely understood. Experimental evidence suggests that at least three mechanisms are involved in the pathogenesis of the migraine headache: extracranial arterial vasodilation, neurogenic inflammation, and decreased inhibition of central pain transmission. Furthermore, cortical spreading depression, a phenomenon involving a slowly progressive wave of depolarization fol-

lowed by electrical silence and hypoperfusion to the cerebral cortex, may play a role in migraine with aura. Research advances using transcranial stimulation and biochemical analysis have provided convincing evidence that no single theory alone can yet explain the onset, maintenance, and resolution of migraine headaches.

According to the vasospasm–vasodilation theory, changes in both intra- and extracranial arterial diameter mediate the symptoms of migraine. Oligemia through extracranial vessels (e.g., the frontal branch of superficial temporal artery) becomes evident during the headache's prodrome and persists into the early headache phase. As the pain phase begins, vessel diameters and cerebral blood flow increase. The resulting hyperemia may persist throughout the duration of the pain phase. Compression of the superficial temporal or carotid artery during this phase has occasionally provided mild pain relief. This headache model prompted trials of peripheral vasoconstricting agents as a pharmacologic means to control migraine-induced

pain. Vasoconstrictors and antiplasma extravasation agents such as caffeine, serotonergic 5-HT_{1B/1D} receptor agonists (triptans), and the nonselective serotonergic agonists (ergot alkaloids) have all been used acutely with variable success in treating migraine.

The trigeminoneurovascular theory describes a complex neurophysiologic system that may contribute to migraine pathogenesis when dysfunctional. Intracranial connective tissues such as the dura and leptomeninges, as well as dural and large intracerebral vessels appear to receive innervation from trigeminal nerve (nociceptive) afferents. Afferent fibers, both unmyelinated (c) and minimally myelinated (A δ), transmit signals to the trigeminal ganglion and dorsal horn trigeminal nuclei. Changes in the vascular compartment may trigger trigeminal nociceptive firing, particularly when trigeminal nociceptive thresholds are lowered.

Autonomic pathways via the facial nerve efferents, mediated through the pterygopalatine and otic ganglia, may alter both intra- and extracranial vascular tone, resulting in vasodilation. Numerous neuropeptides released from parasympathetic nerve terminals are believed to affect vascular smooth muscle contraction. Of these, vasoactive intestinal polypeptide (VIP) has been histologically demonstrated within the terminal nerve endings associated with extracranial vessels supplying the tongue, salivary gland, and nose.^{11,12} Antibodies directed against VIP appear to block the neurogenic vasodilatory response following electrical stimulation of the locus

ceruleus or pterygopalatine ganglion. In addition, VIP release into the extracranial circulation has been observed following trigeminoneurovascular stimulation.¹³

Neuromodulators have also been found in the cell bodies of trigeminal nerve afferents, particularly near the trigeminal ganglion. The neurogenic inflammation theory attributes ongoing pain to peripheral sensitization and chemosensitization. These inflammatory events appear to be regulated by neuropeptide release from trigeminal afferents. Substance P and calcitonin gene-related peptide (CGRP) are among those that have been studied.¹⁴ Serum levels of CGRP taken from the external jugular vein during the headache phase of migraine are elevated.¹⁵ Similarly, stimulation of the trigeminal ganglion as well as the superior sagittal sinus (both of which induce headache when stimulated) releases CGRP into plasma.¹⁶ These inflammatory mediators, along with histamine and neurokinin A, may subsequently create a cascade of events including plasma extravasation, mast cell degranulation, and further vasodilation.

Central pain modulators in the central nervous system (CNS) also appear to exert influence on headache. Although the exact mechanisms are unclear, it appears that neurotransmitter release may affect pain thresholds by increasing or decreasing responses to afferent nociceptive signals. Clinical evidence also suggests that serotonergic hyperactivity in the CNS modulates pain processing in the brainstem.¹⁷ Astrocytes and glial supportive cells have been purported to affect central pain transmission. It is

Table 14.3 Important Headache Descriptors to be Elicited

<i>Age of Headache Onset</i>	<i>Childhood, Juvenile, or Adult Onset</i>
Progression of headache through present time	Stable course, gradually worsening
Frequency and duration of attacks	Daily headache, brief or prolonged episodes
Severity of headache episodes	Nuisance versus severely incapacitating
Quality of the pain	Dull, sharp, throbbing, aching, electrical
Presence or absence of aura	Scotomata, dysesthesias, sensorimotor disturbances
Inciting factors	Head/neck position, chewing, menstruation, weather changes, certain foods
Mitigating factors	Medications, stress relief, sleep, preference for dark, quiet location
Systemic reactions	Nausea, fever, visual changes, syncope, lacrimation, photo-/phonophobia, nasal congestion
Craniofacial disorders	Head or neck trauma, meningitis, subarachnoid hemorrhage, craniofacial surgery
Systemic illnesses	Hypertension, diabetes, venereal disease, psychiatric illness
Medication history	New medications, dosing changes, adverse effects, vasodilator/ vasoconstrictor use
Family history of headache	First- and second-degree relatives, congenital
Social history	Drug use, smoking, alcohol ingestion, occupation, financial or marital stress

likely that a combination of complex interactions, both peripherally and centrally, yield a final common pathway of neurovascular irritation and CNS signal modification.

■ Headache Interview

The correct diagnosis of patients presenting with chronic head and facial pain requires a systematic approach to obtaining the necessary information. At times this may be difficult because the patient's global anxiety, feelings of helplessness, and other mood disorders may complicate the physician's findings. A careful interview and documentation of the complete headache history and examination can aid in reaching the cor-

rect diagnosis and classification. **Table 14.3** highlights important headache descriptors to be elicited.

■ Headache Examination

Although the patient may complain primarily of cranial discomfort, a complete physical examination is warranted on the initial headache visit. Examinations limited to the areas of perceived pain may miss cardiovascular, ophthalmologic, or neuromuscular findings. The ears, nose, throat, scalp, and neck should be thoroughly examined as well.

Specific aspects of the physical examination that may reveal subtle findings to help narrow the differential diagnosis include the following¹⁸:

- Vital signs and affect
- Cardiopulmonary evaluation
- Auscultation of the carotid, vertebral arteries, cranium, and orbits for bruits
- Range of motion, tenderness, crepitus of the neck and jaw/ temporomandibular joint (TMJ)
- Palpation of the head, neck, and back for trigger points, masses, bruises, or thickened or tender blood vessels
- Examination for evidence of papilledema and focal neurologic signs (e.g., visual field deficits and pupillary asymmetry; sensory deficits of the face, trunk, or extremities; asymmetric gait or motor weakness) indicating possible organic etiologies

Ancillary tests may provide the physician with additional clinical information to assist in diagnosis. Neuroimaging, in the form of computed tomography (CT) or magnetic resonance imaging (MRI), has become an invaluable resource for physical diagnosis among multiple medical specialties. Continuing technologic advances allow for improved quality and greater access to an array of imaging modalities. Lumbar puncture (LP) may be indicated during a severe headache to detect subarachnoid hemorrhage or meningitis, and can be diagnostic of meningeal carcinomatosis or lymphomatosis, and to detect high or low cerebrospinal fluid (CSF) pressure.¹⁹ Electroencephalography (EEG) had been used historically to screen for structural cerebral abnormalities via the detection of altered electrophysiologic patterns, thereby warranting further diagnostic

evaluation with imaging. But in 1995, the American Academy of Neurology failed to find sufficient evidence supporting the utility of EEG in the routine evaluation of headache.²⁰ It recommended CT or MRI if clinical evidence suggested the possibility of organic brain pathology.

■ Treatment Approach

Migraine

The effective treatment of migraine headache involves implementing an abortive therapy for the acute attack (acute therapy) as well as developing a rational strategy to prevent or minimize future migraine episodes (preventative therapy).²¹ Acute therapy aims to rapidly and effectively lessen the severity of the acute migraine and restore patient comfort and function. The goals of preventative therapy are to reduce the severity, frequency, and duration of future episodes. In addition, preventative therapy should help increase responsiveness to acute medications, improve patient function, and reduce disability from disease.²¹ Preventative therapy should be implemented if any of the following conditions are met: poor response to acute therapy alone, adverse reaction or contraindication to acute therapy, exhaustion of acute therapy modalities, severe functional disability from recurrent episodes, high frequency of recurrent episodes, or the presence of a comorbid condition requiring long-term migraine control. A comprehensive approach generally includes both pharmacologic and

Table 14.4 Commonly Used Abortive Medications

Nonsteroidal antiinflammatory drugs (NSAIDs)
Ibuprofen
Aspirin
Sodium naproxen
Analgesics
Opiates/barbiturates
Acetaminophen
Vasoconstrictors
Caffeine
Sympathomimetics
Isometheptene
Serotonergics
5-HT _{1B/1D} selective (triptans)
Nonselective (ergots alkaloids)

nonpharmacologic therapy such as avoidance and biofeedback.

Abortive Therapy

Abortive therapy aims to provide full relief of symptoms within a few hours of initiation of treatment. The acute treatment serves both a humanistic as well as a medical role. From a humanistic perspective, abortive therapy eases patient suffering and reduces the strain on interpersonal relationships and professional productivity. From a medical perspective, it appears to interrupt the progression from the acute migraine headache to a chronic debilitating disorder.²² **Table 14.4** gives commonly used abortive medications.

The following sequence outlines a typical stepwise treatment protocol for migraine²³:

1. A nonsteroidal antiinflammatory analgesic
2. Step 1 plus a mild vasoconstrictor
3. Steps 1 and 2 plus codeine or a barbiturate or a change of analgesic

4. Oral triptan
5. Intranasal or subcutaneous triptan
6. Alternatively, use an intranasal, rectal, or subcutaneous ergot

Preventative Therapy

The goal of headache prevention therapy is to limit the severity, duration, and frequency of episodes, so that ultimately the patient's quality of life improves. Both pharmacologic and nonpharmacologic interventions play a role. The choice of which agent or combination of agents to use depends on the patient's comorbid medical conditions, adverse effect profile, physician preference, and cost. Nonpharmacologic approaches including exercise, dietary adjustment, and biofeedback therapy continue to play an important role in migraine management. They not only are effective for headache prevention, but also may reduce the impact of comorbid psychological disturbances.

The United States Headache Consortium recently issued an evidence-based review of the pharmacologic agents used

Table 14.5 Medications with Demonstrable Efficacy

<i>Group 1</i> Divalproex sodium (anticonvulsant) Propranolol, timolol (beta-blocking agents) Amitriptyline (tricyclic antidepressant)
<i>Group 2</i> Atenolol, metoprolol, nadolol (beta-blocking agents) Nimodipine, verapamil (calcium channel blockers) Aspirin, naproxen, naproxen sodium, mefenamic acid (NSAIDs) Gabapentin (γ-aminobutyric acid [GABA] receptor blocker), guanfacine (α₂-receptor agonist) Feverfew, magnesium, and vitamin B₂
<i>Group 3</i> Nortriptyline, protriptyline, doxepin, and imipramine (tricyclic antidepressants) Fluvoxamine, paroxetine, and sertraline (selective serotonin reuptake inhibitors [SSRIs]) Bupropion, mirtazapine, trazodone, and venlafaxine (miscellaneous antidepressants)
<i>Group 4</i> Methysergide, dihydroergotamine (serotonin antagonists)

to prevent migraine.²¹ Medications were classified according to the level of evidence to support their efficacy and safety in headache prevention. Medications in group 1 have demonstrated excellent efficacy, whereas those in group 5 have little or no proven efficacy. Examples of medications with at least some demonstrable efficacy (groups 1 to 4) are listed in **Table 14.5**.

■ Pharmacology of Botulinum Neurotoxin

Pharmaceutical agents currently available to treat migraine have largely proved unsatisfactory because of limited efficacy, intolerable adverse effects, and drug interactions. BoNT/A is a paralytic neurotoxin that inhibits acetylcholine (ACh) release at the neuromuscular junction. Although it has been approved for treating blepharospasm, strabismus, cervical dystonia, hyperhidrosis, upper

limb spasticity, and hyperfunctional glabellar lines, it has been safely used to treat various dystonias, spasticity, and tremor of the head and neck. BoNT/A's role as a useful antinociceptive agent for headache disorders was derived from anecdotal reports of patients being treated for hyperfunctional facial lines. Incidentally, these patients reported reductions in the frequency and severity of headache episodes and facial tension.²⁴ These findings have been reproduced in several clinical studies for migraine headache.^{25–27}

In addition to its effects at the neuromuscular junction (NMJ), BoNT/A has also been shown to block acetylcholine release at parasympathetic nerve terminals, as evidenced by its efficacy in treating sialorrhea and hyperhidrosis. It is unclear how BoNT/A relieves headache, but various possible mechanisms have been suggested. These include direct effects at the neuromuscular junction and direct antiproprioceptive effects on

nerves of the head and neck. Guyuron et al²⁸ proposed that migraine may be triggered by cranial muscle contraction, particularly the corrugator muscles, which stimulate trigeminal nociceptors passing through the muscle. Smuts et al²³ concluded, however, that migraine headache relief following BoNT chemo-denervation of the corrugator muscles surpassed the time course of muscle denervation, suggesting that alternate pathways for pain relief must exist. Recent evidence suggests that BoNT/A may also inhibit the release of various neuropeptides and neuromodulators such as substance P, glutamate, and CGRP, thereby blocking the transmission of afferent nociceptive signals to the central nervous system.²⁹

■ Technical Aspects

Dosage and Dilution

There are currently three formulations of BoNT/A (Botox, Dysport, and Xeomin) and one type B complex (Myobloc) approved for clinical use and currently available in the United States for injection. These toxin types have different dosing and safety parameters, and thus familiarity with each toxin is essential prior to administration. Currently, there are no well-established methodologies to calculate equivalent doses.³⁰

OnabotulinumtoxinA (Botox; Allergan, Inc., Irvine, CA) was the first type A toxin available in the United States. Each vial contains 100 units (U) of powdered BoNT/A, and requires dilution with 0.9%

nonpreserved saline. We typically dilute each vial with either 2 or 4 mL of saline to prepare a 5.0- or 2.5-U per 0.1-mL stock, respectively. AbobotulinumtoxinA (Dysport; Medicis Pharmaceutical, Scottsdale, AZ) is available in 500-U bottles, and incobotulinumtoxinA (Xeomin; Merz Pharmaceuticals, Greensboro, NC) is available in 50- and 100-U bottles.

RimabotulinumtoxinB (Myobloc; Solstice Neurosciences, Inc., South San Francisco, CA) is available in 2500- and 5000-U/mL vials and is prediluted with 0.05% human serum albumin.

There are no treatment guidelines regarding the optimal dilution of BoNT/A for headache disorders. Our clinical experiences have indicated a greater overall response utilizing lower concentrations at multiple sites with larger injection volumes (e.g., 2.5 U/0.1 mL) as opposed to higher concentrations at fewer sites with smaller injection volumes.³¹ Due to the large surface areas affected by the headaches, multiple injection sites are often necessary. The number of injection sites varies in the literature from four to as many as 25. The total dose administered is often individualized, taking into consideration the severity of symptoms, body habitus, and headache type. Total injection doses of between 15 and 150 U have been reported.

Injection Technique

Botulinum neurotoxin injection for headache is administered using either a fixed position or a follow-the-pain technique, depending on the headache type and

physician's examination. Migraine headaches typically respond well to the fixed-position technique, whereas tension-type headaches (TTHs), because of the variability in presentation, often are treated with the follow-the-pain approach.²⁵ Patients exhibiting mixed features of migraine and TTH often require a combination of both techniques.

Following the initial dilution, the toxin is drawn into a 1-mL syringe with a 30-gauge needle attached. Sterile technique is used during both toxin preparation and administration. The patient is typically placed in a reclined position and the skin cleansed with alcohol to remove debris and contaminants. By limiting injections to the subcutaneous tissue or muscle belly, injection-related pain and risk of bruising is lessened. Electromyographic (EMG) guidance is helpful, particularly when directing the toxin into the larger, deeper muscles of the temporal and occipital scalp. Injecting into the periosteum on the forehead or glabella often causes unnecessary pain.³²

The target muscles for the fixed-site approach include those of the glabellar region, forehead, temporal area, and occipital region (if occipital pain is present). Specifically, the procerus, corrugator, frontalis, and temporalis muscles are isolated. Our protocol for BoNT/A injection includes the procerus muscle (5 U, one site), corrugator muscle (2.5 U each site, two sites [medial and lateral] on each side), frontalis (2.5 U each site, five sites on each side), and temporalis muscle (2.5 U each site, four sites on each side)²⁶ (**Figs. 14.1 and 14.2**). When

using the follow-the-pain approach, we have found that injections into the frontalis, temporalis (doses as above), and, depending on pain localization, the trapezius (7 to 15 U on each side), splenius capitis/ semispinalis capitis (5 to 15 U per side, one to two sites on each side), and occipitalis (2.5 to 5 U per side) muscles are often necessary (**Fig. 14.3**).³³ In addition, patients with temporomandibular disorder or anterocollis may benefit from BoNT injection to the masseter or sternocleidomastoid muscles, respectively.

Injections of the forehead and glabellar region should be performed symmetrically, using smaller injection volumes, to avoid facial asymmetry or diffusion to unwanted sites. Intramuscular injections of the temporalis, occipitalis, masseter, sternocleidomastoid, and paraspinal muscles require larger injection volumes, need not be symmetric, and are typically guided by patient symptomatology.

■ Anatomic Targets

Corrugator Supercilii Muscle

This thin muscle lies just above the supraorbital rim in an oblique direction toward the nasal dorsum. Deep to the lateral aspect of the muscle, the supraorbital neurovascular bundle exits the skull, whereas the supratrochlear nerve and vessels exit medially. The muscle depresses the medial brow and often creates vertical frown lines over the glabellar region when hyperactive. The muscle can be identified while the patient

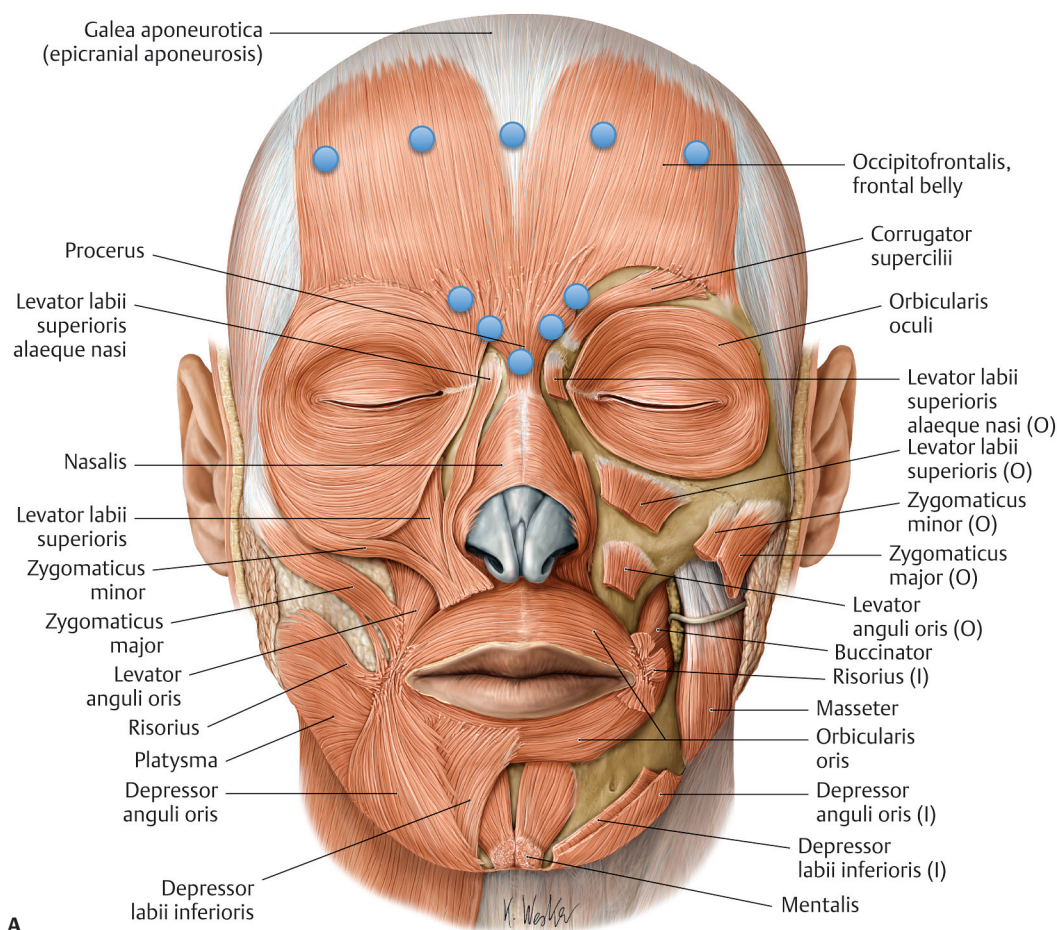


Fig. 14.1 (A) Glabellar and forehead injection sites. (From Atlas of Anatomy, © Thieme 2008, Illustration by Karl Wesker.)

frowns, allowing the physician to gently grasp the muscle belly to facilitate a precise injection (**Fig. 14.1**).

Procerus Muscle

This small triangular muscle is continuous with the inferior extension of the frontalis muscle in the midline. It passes from the lower forehead over the bridge of the nose, where it attaches to the skin overlying the glabella. It functions as a medial brow depressor, producing a

typical horizontal frown line over the nasal bridge when hyperactive. Injections are directed in the midline toward its muscular base (**Fig. 14.1**).

Frontalis Muscle

This large broad muscle extends superiorly over the cranium from the supra-orbital rim to the parietal region. Hyperfunctional frontalis muscles create horizontal forehead lines, most notable during eyebrow elevation. Proper injection



Fig. 14.1 (B) Injection of the glabella and forehead.

tion technique involves broad application to the superior and middle aspects of the muscle. Injections directed toward the lower lateral portion of the frontalis may result in brow ptosis (**Fig. 14.1**).

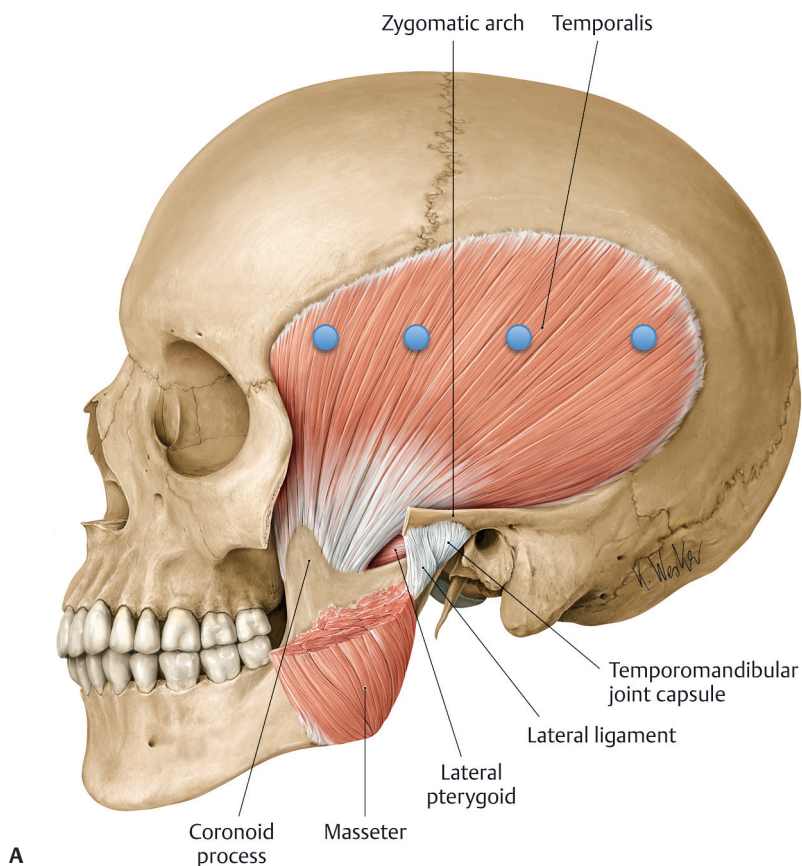
Temporalis Muscle

This large fan-shaped muscle covers the lateral aspect of the cranium, originating from the temporal line and inserting on the coronoid process of the mandible. While palpating the temporal area, larger bundles of muscle can be identified by having the patient clench his or her teeth. Injections are typically administered as 5 U per 0.2-mL aliquots at four distinct sites throughout the muscle. Because of the large size of the muscle, a larger volume may be admin-

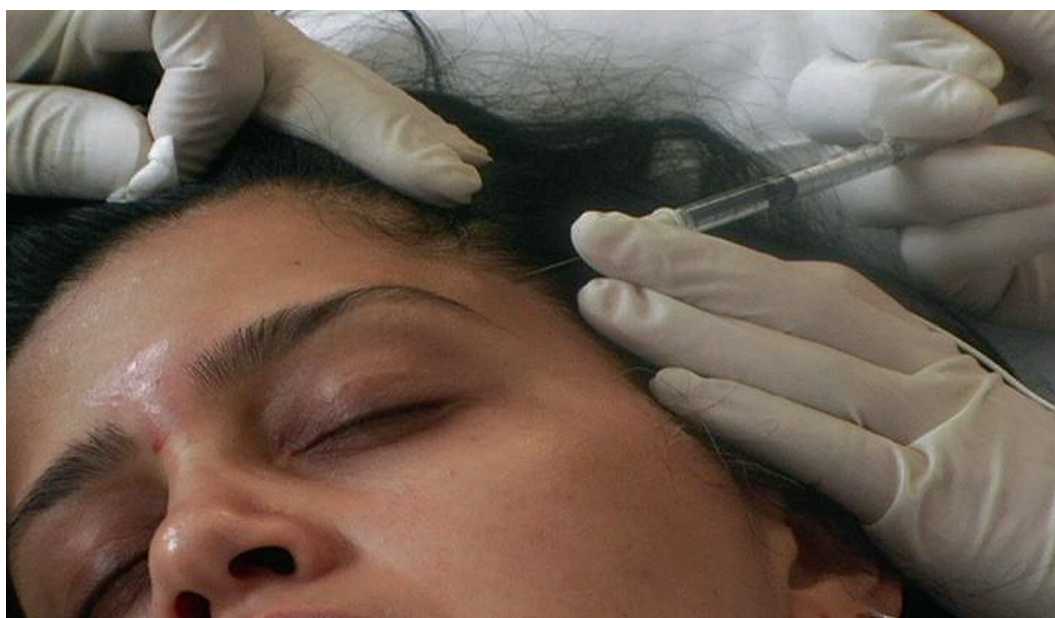
istered without affecting adjacent structures³³ (**Fig. 14.2**).

Other Muscles

Muscles of the posterior scalp, cervical region, and upper back may be treated as part of a fixed-site approach, or based on patient report or the presence of tenderness to palpation. Pain may be present at the occipital region (lateral to the protuberance) or paraspinal area adjacent to the nuchal line. Within this region, the trapezius muscle, splenius capitis, and semispinalis muscles converge (**Fig. 14.3**). Precision is not crucial within this region, and larger doses (5 to 15 U per area) and injection volumes are acceptable, as extravasation will improve the toxin's regional penetrance.



A



B

Fig. 14.2 (A) Temporal region injection sites. (From Atlas of Anatomy, © Thieme 2008, Illustration by Karl Wesker.) **(B)** Temporal injection.

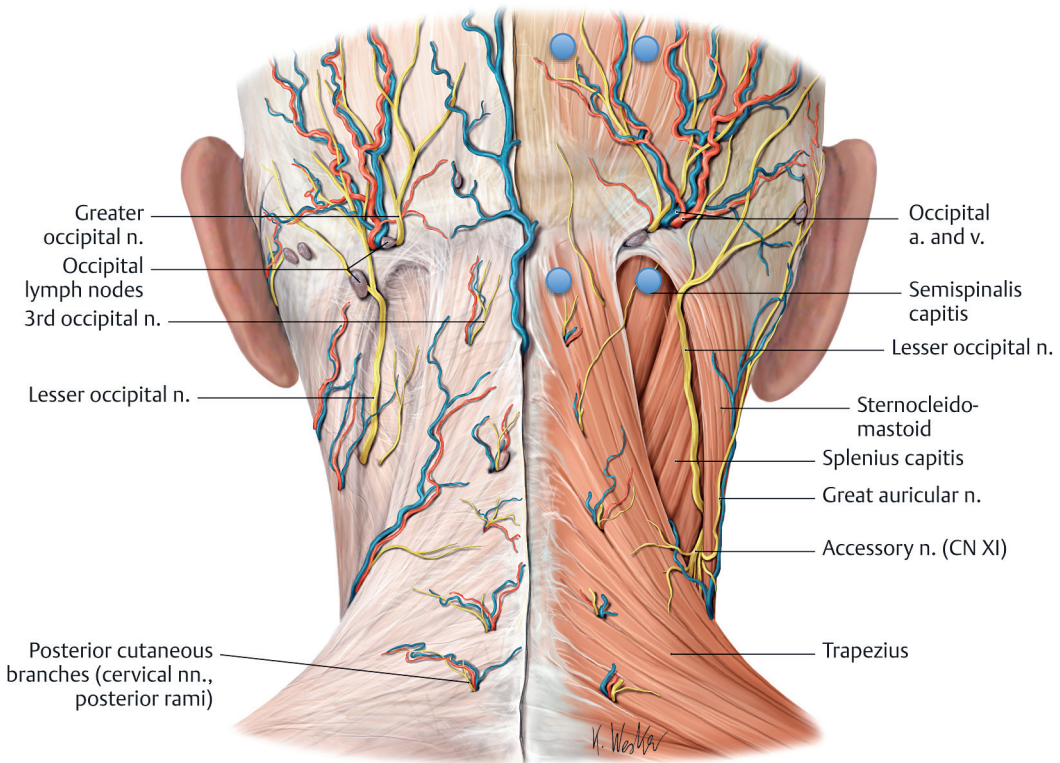


Fig. 14.3 Occipital and paraspinal injection sites. (From Atlas of Anatomy, © Thieme 2008, Illustration by Karl Wesker.)

■ Risks and Hazards

Adverse effects of BoNT injection are often mild or transient, and can usually be minimized through proper injection technique. Most local complications result in cosmetic asymmetry; however, paresis of periorbital muscles when treating the upper face may result in visual disturbances. Effects reported during the treatment of headache disorders include blepharoptosis, brow ptosis, diplopia, and muscle weakness at the site of injection.³⁴ Various minor sequelae are also discussed in the following subsections.

Eyelid Ptosis (Blepharoptosis)

Although few occurrences of eyelid ptosis have been reported following BoNT treatment for migraine headaches, the physician should exercise caution when injecting the corrugator muscles. Eyelid ptosis results from toxin extravasation through the superior aspect of the orbital septum, causing paralysis of the levator palpebrae superioris muscle. The risk of eyelid ptosis increases if injections are placed at or under the middle of the eyebrows in the vicinity of the midpupillary line.³² This can be problematic in elderly patients with reduced orbital septum integrity. The onset may

occur 2 to 10 days following injection and persist for up to 2 to 4 weeks before resolution. Utilizing smaller injection volumes, maintaining digital pressure at the superior orbital rim during injection, and placing injections at least 1 cm above the supraorbital rim at the midpupillary line may reduce the risk of ptosis.³¹ Should ptosis occur, mydriatic eyedrops (e.g., 2.5% phenylephrine hydrochloride) three times daily until symptoms resolve reduce the severity of dysfunction.³⁵

Brow Ptosis

Brow ptosis may result from inferolateral frontalis (lateral brow ptosis) or supra-orbital frontalis weakness (middle brow ptosis). The frontalis muscle serves to elevate the eyebrow; hence, an overly weakened frontalis muscle can result in brow droop. Proper injection technique is essential to avoiding brow ptosis. Injections are targeted at least 2 cm above the supraorbital rim, and up to 4 cm in patients with low-set brows.³² Not rendering the frontalis muscle completely immobile, but rather weakened, can achieve a comparable goal while maintaining some forehead movement. Correction involves BoNT injection to either the ipsilateral superolateral orbicularis oculi muscle (lateral depressor) or corrugator and superomedial orbicularis oculi muscles (medial depressors) depending on the presentation.

Diplopia

Diplopia is a disabling but fortunately rare complication when treating headache. It has historically been associated with treating hyperfunctional periorbital

lines, or “crow’s feet.” Double vision may result from toxin migrating beyond the orbital septum to the lateral rectus muscle within the orbit. The orbicularis oculi muscle surrounds the palpebral fissure circumferentially, extending beyond the orbital rim just deep to the subcutaneous tissue. Carefully injecting the orbicularis just below the epidermis, 1 cm outside the orbital rim or 1.5 cm lateral to the lateral canthus, should help prevent diplopia.³² Directing the needle away from the orbit to prevent extravasation of toxin toward the globe is prudent. Diplopia warrants an immediate ophthalmologic referral.

Minor Adverse Effects

Infrequent minor sequelae from the use of BoNT injection at any site include pain, erythema, swelling, bruising, and short-term hypoesthesia. The immediate application of an ice-pack before or after intramuscular injection may reduce the pain, edema, and localized erythema. Patients are instructed to avoid aspirin, nonsteroidal antiinflammatory drugs (NSAIDs),³² and vitamin E for 1 week prior to injection. Small subcutaneous vessels can often be avoided visually, whereas larger vessels may be identified via palpation. Pain can be minimized by infusing slowly with a 30- or 32-gauge needle directly into the muscle belly, avoiding the periosteum.

■ Postinjection Care

Headache relief from BoNT/A may take several weeks to reach maximal effect.

Having the patient keep a headache diary documenting the time, severity, duration, and frequency of all headache events helps the physician to modify future injection dosages.³³ Any medications taken to relieve acute breakthrough headaches should be noted. Adverse effects and suboptimal outcomes are assessed at a 4- to 6-week follow-up examination, and additional BoNT may be injected at that time.

Repeated injections are necessary as the botulinum effect subsides. There is tremendous variation among patients with respect to injection frequency. Some patients experience relief well beyond the predicted pharmacokinetic duration of the drug, suggesting a possible neuromodulating effect of the toxin within the CNS. The authors have also found that the response to toxin injection may change over time, with some patients reporting greater therapeutic effect with repeat injections.²⁷ Although many patients require repeat injections at 3- to 4-month intervals, personalized headache diaries help in directing treatment needs.

■ Success with Botulinum Neurotoxin

Clinical evidence supporting the use of BoNT injections for migraine headache is mixed. In Binder et al's²⁷ open-label study, 51% of migraine sufferers reported complete responses, and an additional 38% reported partial responses. Complete responders reported a mean benefit of 4.1 months, whereas partial responders benefited for 2.7 months. Furthermore, 70% of patients treated acutely for mi-

graine pain reported complete response. In another study, patients were categorized according to headache type, including migraine, episodic TTH, mixed headache, and chronic daily headache. Patients were treated with prophylactic BoNT injections in the manner previously described. Overall, the number of headache days per month was reduced 56%, the headache intensity score dropped 25%, and 86% of patients reported improvement in headache intensity and frequency.²⁵ More recently, however, large double-blind studies have failed to demonstrate a significant benefit of botulinum neurotoxin injection for episodic migraine prophylaxis over placebo.^{36–38} Nevertheless, interest in botulinum neurotoxin as a prophylactic therapeutic agent for headache continued, particularly in chronic migraine. Pooled results from the multicenter placebo-controlled PREEMPT (Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy) trial demonstrated a significant benefit of onabotulinumtoxinA over placebo in reducing the frequency of headache days/episodes, migraine days/episodes, triptan intake, and percentage of patients with chronic migraine headache.³⁸

■ Conclusion

Migraine is a leading cause of disability in the United States. Chronic pain and associated symptoms interfere with professional and interpersonal relations, and reduce quality of life. In addition, headache sufferers show an increased risk of psychiatric disorders, such as depression and anxiety. The socioeconomic

burden of headache is significant, which is troubling in light of the current health care crisis. Physicians have the unique opportunity to diagnose and effectively treat headache disorders and ease patient suffering. A comprehensive headache examination should allow the physician to classify the specific disorder and initiate an effective therapeutic plan.

Medications currently available for migraine headache have demonstrated variable efficacy and an often unacceptable adverse-effect profile. Botulinum neurotoxin, through poorly understood

pathways, may provide relief from headache pain and reduce the severity, frequency, and duration of recurrent episodes, particularly in chronic migraine. Adverse effects from BoNT are often mild, transient, and related to adjacent muscle weakness. These effects can often be avoided by the use of proper injection technique. Through fixed-site or follow-the-pain injection techniques, migraine headache relief for 4 months or longer has been observed. BoNT therapy appears to be a safe and effective adjunct in migraine therapy.



Video 19 Migraine

In this patient with left temporal and postocular pain, the area of the glabella (supraorbital and supratroclear nerves) is injected in three places with 2.5 U/0.1 cc at each point as shown. The left anterior temporalis muscle is also injected with 2.5 U/0.1 cc of Botox in 3 to 5 different sites.

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Chronic Tension Headache

Nwanmegha Young and Brian E. Benson

Tension-type headache (TTH) is the most common form of headache. It is sometimes referred to as “stress headache” or “muscle tension headache.” There are two classifications of TTH: episodic tension-type headache (ETTH), which occurs randomly and infrequently, and chronic tension-type headache (CTTH), which occurs daily or continuously on at least 15 days per month, although the intensity of the pain may vary during a 24-hour cycle.¹ It is estimated that 30 to 80% of the adult population in the United States suffers from occasional TTH, yet only 3% suffer from CTTH.²

Symptoms of TTH include a tight feeling in head or neck muscles or a tightening band-like sensation around the neck or head, which creates a “vise-like” ache. The pain is typically found in the forehead, temples, or the back of the head or neck. However, there is frequently significant crossover between the symptoms of TTH and migraine without aura. In fact, in the Spectrum study, 71% of the

participants initially diagnosed with episodic TTH subsequently had their diagnosis changed to migraine or migrainous headache after their headache diary was reviewed by the investigators.³ The second edition of the International Classification of Headache Disorders (ICHD-II) subdivides TTH into three divisions: infrequent episodic, frequent episodic, and chronic⁴ (**Tables 15.1** and **15.2**). The etiology of TTH is thought to be related to cervical myofascial activity involving the neck, face, and scalp, which likely reflects a complex syndrome involving peripheral nociceptors in ETTH and central dysnociception in CTTH.¹

Nonpharmacologic treatments such as relaxation and electromyography (EMG) biofeedback therapies, cognitive behavioral interventions, and various physical therapy techniques have shown various degrees of success at reducing the frequency and severity of TTH. Medications used to treat chronic daily headache include simple analgesics, such as

Table 15.1 Tension-Type Headache (Episodic Form)—General Diagnostic Criteria B–E

- B. Headache lasting from 30 minute to 7 days
- C. At least two of the following pain characteristics:
 - 1. Bilateral location
 - 2. Pressing or tightening (nonpulsating) quality
 - 3. Mild or moderate intensity
 - 4. Not aggravated by routine physical activity, such as walking or climbing stairs
- D. Both of the following:
 - 1. No nausea or vomiting (anorexia can occur)
 - 2. No more than one of photophobia or phonophobia
- E. Not attributed to another disorder

(From International Headache Society. The International Classification of Headache Disorders, 2nd ed (ICHD-II). Cephalalgia 2004;24(suppl 1): 9–160. Reprinted by permission.)

aspirin and paracetamol, and nonsteroidal antiinflammatory drugs (NSAIDs), such as ibuprofen and naproxen sodium. The addition of caffeine increases the efficacy of these medications. Prophylactic medications such as tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), the antispasmodic drug

tizanidine, and topiramate may provide additional relief for some patients. Unfortunately, current pharmacotherapy for CTTH can be limited by either incomplete efficacy or intolerable side effects.

Given its effects on nociception and muscle contraction, botulinum neurotoxin (BoNT) appears to be an attractive

Table 15.2 Tension-Type Headache—Specific Diagnostic Criteria

- 2.1 Infrequent episodic tension-type headache
 - A. At least 10 episodes that occur on less than 1 day per month (less than 12 days per year) that fulfill criteria B–D
- 2.2 Frequent episodic tension-type headache
 - A. At least 10 episodes that occur on one or more days per month but less than 15 days per month for at least 3 months (12 or more days and less than 180 days per year) that fulfill criteria B–D
- 2.3 Chronic tension-type headache
 - A. Headache that occurs on 15 or more days per month, on average for more than 3 months (180 or more days per year) that fulfills criteria B–D
 - B. Headache that lasts hours or may be continuous
 - C. Both of the following:
 - 1. No more than one of photophobia, phonophobia, or mild nausea
 - 2. Neither moderate nor severe nausea nor vomiting
- 2.4 Probable tension-type headache
 - A. Episodes that fulfill all but one of criteria A–D for 2.1, 2.2, or 2.3
 - B. Episodes that do not fulfill criteria for 1.1 (migraine without aura)
 - C. Not attributed to another disorder

(From International Headache Society. The International Classification of Headache Disorders, 2nd ed (ICHD-II). Cephalalgia 2004;24(suppl 1): 9–160. Reprinted by permission.)

Table 15.3 Tension-Type Headache Candidates for Botulinum Neurotoxin Type A Therapy

Patients who have failed to respond adequately to conventional treatments
Patients with unacceptable side effects from existing treatment
Patients in whom standard preventive treatments are contraindicated
Patients who are misusing, overusing, or abusing medications
Patients with spasm or trigger points involving the jaw, head

agent in the prophylaxis of TTH. In addition to its well-known effects in reducing muscle contractions, it may also block the release of pain mediators such as substance P, glutamate, and calcitonin gene-related peptide.⁵ Our experience with temporomandibular disorder (TMD) patients with TTH shows a 70% response rate (where a response is a 50% or greater reduction in intensity or frequency of headache) in an open-label study. Early, nonrandomized series provided encouraging data supporting the role of prophylactic treatment with BoNT/A.⁶ The results of the PREEMPT (Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy) trials 1 and 2 strongly supported the use of BoNT/A for chronic migraine prophylaxis.^{7,8} Given the significant crossover between the symptoms of TTH and migraine, a plausible mechanism for BoNT/A prophylaxis of TTH was established. In contrast, the results of more recent, randomized, controlled trials for the efficacy of BoNT in the prophylactic treatment of TTH are negative.^{9,10}

However, these findings do not rule out a possible role of BoNT/A in patients with severe, unremitting forms of CTTH, especially those with severe, mixed forms

of these headaches, and patients with myofascial trigger points, or significant TMD (**Table 15.3**).

■ Workup

The diagnosis of TTH is based on a comprehensive history and neurologic examination, frequently in conjunction with a headache diary, and imaging studies. The diagnostic criteria for TTH are listed in **Tables 15.1 and 15.2**.

■ Anatomy

The pertinent anatomy is reviewed in Chapter 14.

■ Technique

There are no formal clinical guidelines for the use of BoNT in the treatment of headaches. Based on our experience, we typically employ one of two typical approaches to injecting BoNT to relieve headache pain. The “fixed-site” approach is typically employed in patients with migraine features, whereas the “follow-

the-pain” approach is typically used for patients with TTHs. Both approaches can be combined for patients with features of mixed headache.

Fixed-Site Approach

Botulinum neurotoxin type A is injected into the procerus (5 units [U], one site), corrugator (2.5 U each, two sites [medial and lateral]), frontalis (2.5 U each, five sites on each side), and temporalis (2.5 U each, four sites on each side) muscles. Although “blind” injection technique may be used, we find that EMG guidance is useful to help target the appropriate muscles, especially the thin temporalis muscle.

Follow-the-Pain Approach

Using EMG guidance, BoNT/A is injected into the frontalis (2.5 U each, five sites on each side), temporalis (2.5 U each, four sites on each side), occipitalis (2.5 to 5 U on each side), trapezius (7.5 to 15 U on each side), semispinalis capitis (7.5 to 15 U on each side), and/or splenius capitis muscles, as deemed appropriate.

Follow-Up

If effective, injections are typically repeated every 3 to 4 months, as necessary.

Complications

Ptosis of the eyelid and the eyebrow have been reported in less than 2% of patients. Other reported potential complications include neck weakness, bruising, and flu-like symptoms.

Conclusion

Clinical and preclinical studies performed to date suggest that BoNT/A may work at multiple points in the pathophysiologic cascade of headache, although it is not yet clear which of these points are quantitatively most important. Although the efficacy of BoNT/A to ameliorate the symptoms of chronic migraine has been established, further studies need to be performed to determine which, if any, TTH patients will most benefit from BoNT injection.



Chronic Tension Headaches

Most chronic tension headaches are related to a “vise-like” pain across the head. We start with injections of the temporalis muscles bilaterally, as can be seen in Video 18. We also usually inject across the forehead, as outlined in Video 12, on glabellar frown lines. Occasionally patients also have pain in the occiput or along the nuchal lines; these injections can be seen as part of Video 8 on cervical dystonia.

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Trigeminal Neuralgia

***Andrew Blitzer, Lesley French Childs,
and Ronda E. Alexander***

Trigeminal neuralgia (TN), as defined by the International Association for the Study of Pain (IASP), is a unilateral facial pain disorder that is characterized by brief, paroxysmal, sharp lancinating pains that are recurrent, and limited to the distribution of one or more divisions of the trigeminal nerve.¹ The prevalence of this disorder is approximately 1 in 25,000, and it is slightly more common in women than in men. It also affects middle-aged or older people more frequently.²

In the latest classification of the International Headache Society, a distinction was made between classical and symptomatic TN: classical TN (CTN) includes idiopathic cases in addition to those with vascular compression of the fifth cranial nerve; symptomatic TN (STN) is diagnosed in cases secondary to multiple sclerosis, tumors, and structural abnormalities of the skull base.³ The pain

attacks can be either spontaneous, or precipitated by certain cutaneous stimuli within specific “trigger zones,” leaving some patients unable to eat, drink, brush their teeth, or shave. The attacks come in bouts of weeks to months with intervening symptom-free periods. There are usually diurnal variations in symptoms with exacerbations during mornings and characteristic absence during sleep.⁴

Many theories have been proposed to explain the disease process, but a recent leading theory implicates demyelination of the sensory fibers within the proximal nerve root of the trigeminal nerve.⁵ Most cases of trigeminal neuralgia (80 to 90%) have an overlying blood vessel causing compression at the root entry zone. The offending vessel can be the superior cerebellar artery (75%), the anterior inferior cerebellar artery (10%), or a vein.⁶ Focal demyelination within or

near this area has been documented on histologic examination of specimens taken during microvascular decompression in the immediate vicinity of the indentation, with the demyelinated axons found to be in direct apposition.⁷ The A- δ thinly myelinated nociceptive fibers may be particularly vulnerable to such changes.⁸ This pathologic arrangement may lead to abnormal nonsynaptic ephaptic transmission to adjacent fibers.⁹ Moreover, because fibers for light touch and pain are closest in proximity within the root entry zone, this theory provides a ready explanation for the paroxysmal pain provoked by cutaneous stimuli.⁵

Many approaches have been employed to alleviate the pain and reduce the frequency of pain attacks in this disorder. Pharmacotherapy with anticonvulsive drugs remains the first-line therapy. Carbamazepine or oxcarbazepine is often used for pain control. In patients with TN refractory to medical therapy, microvascular decompression, percutaneous approaches to the gasserian ganglion, and the gamma knife may also be considered, depending on surgeon experience and patient preference.¹⁰

Botulinum neurotoxin type A (BoNT/A) has been successfully utilized to treat pains such as migraine and occipital neuralgia as discussed in previous chapters in this book. BoNT/A has recently gained popularity in treating patients with TN, more specifically TN refractory to medical and occasionally surgical treatment.^{11–15}

The mechanism by which BoNT/A exerts its effect in TN is still not well established; however, it is probable that it

eliminates pain through an effect similar to that seen with other pain syndromes. Multiple theories have been proposed to explain this phenomenon, the most recent of which adopts the notion that there is an antinociceptive effect of BoNT in sensory neurons that is separate from its neuromuscular effect as it inhibits the release of neurotransmitters known to elicit the pain response, including substance P, calcitonin gene-related peptide (CGRP), and glutamate.¹⁶ It also reduces peripheral and central sensitization.¹⁷

■ Workup and Patient Selection

The diagnostic workup for patients amenable to BoNT/A treatment should elicit a history of pain that has become resistant to pharmacotherapy, or intolerance to the side effects of the medications. These patients had been previously labeled surgical candidates; however, BoNT/A treatment offers a less invasive option for pain alleviation with good results and minimal side effects.

The history should definitively rule out other causes of facial pain. Because of the association with multiple sclerosis, patients should be asked about neurologic symptoms (e.g., dizziness, focal weakness, ataxia, vision changes) and other atypical symptoms that might lead to another diagnosis.

The physician should perform a careful head and neck examination, with emphasis on the neurologic aspect. An otologic, oral, and temporomandibular joint (TMJ) examination should be done

to search for other causes of facial pain. TN patients usually have a normal neurologic examination, and the finding of trigger points nearly confirms the diagnosis.¹⁸ Documentation of facial nerve function and facial symmetry prior to the injections must be emphasized in the neurologic head and neck examination. Magnetic resonance imaging (MRI) of the brain should be performed for all patients presenting with trigeminal neuralgia, if one has not yet been performed prior to presentation.¹⁰

Absolute contraindications to BoNT use include a known allergy or sensitivity to the toxin, and diseases that might interfere with neuromuscular transmission, such as myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, and others. BoNT should not

be used in pregnant or lactating women or in patients taking aminoglycosides, as these can interfere with neuromuscular transmission.

■ Technique

The identification and treatment of trigger zones on the face will provide the most benefit to the patient. At each visit, it is useful to draw a grid on the patient's face in the region of allodynia or hyperesthesia (**Fig. 16.1**). Next, 2.5 unit (U)/0.1 cc intradermal injections of BoNT per square centimeter are administered within the grid (**Fig. 16.2**). Careful record keeping using a facial map or diagram facilitates administering repeat injections as necessary, although the region of sensitivity is

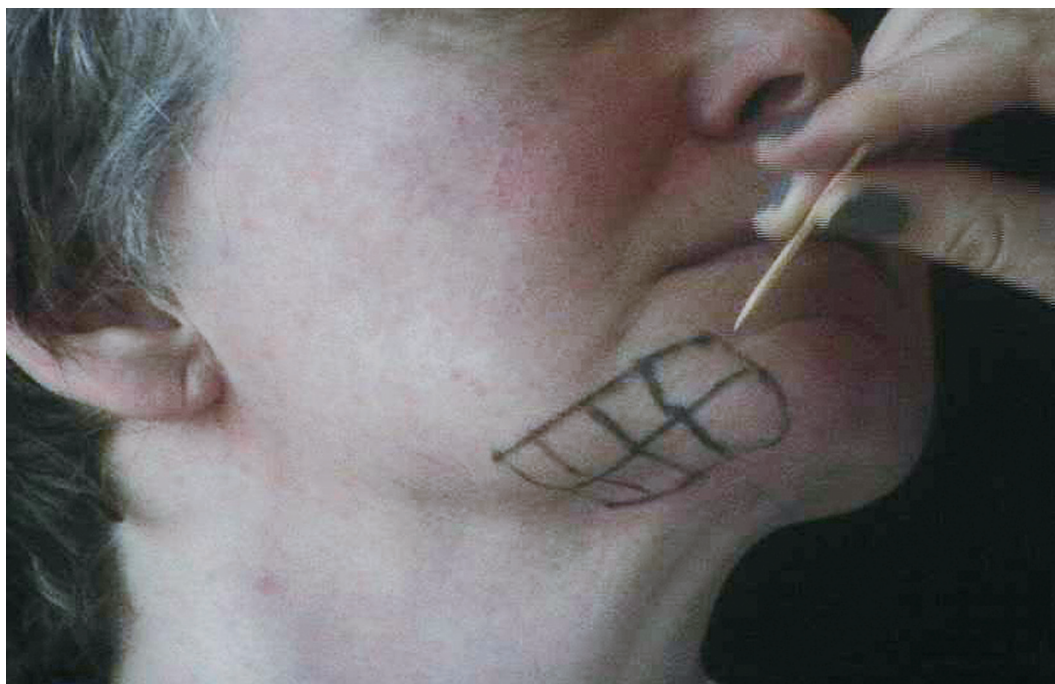


Fig. 16.1 Grid drawn on region of hyperesthesia/allodynia.



Fig. 16.2 Intradermal injection at intersection of grid lines.

likely to change at each visit. The amount of toxin to be injected is tailored to the individual. Wide variations have been published in the literature, with one case report documenting the administration of 100 U to a single trigger site.³

■ Follow-Up

Frequency of administration also needs to be individualized. Duration of effect in the literature ranges from weeks to 6 months. Initial treatments should be accompanied by a pain diary, which enables the patient and physician to track the waning and waxing of symptoms with treatment.

■ Complications and Pitfalls

Side effects of BoNT injections are generally a result of its effect on motor synapses, including the possibility of facial weakness and asymmetry after treatment. Facial edema, erythema, and hypesthesia of the treated regions have also been reported.⁴

■ Conclusion

Botulinum neurotoxin treatment of trigeminal neuralgia represents a safe and effective treatment modality. Further studies will help to clarify ideal injection schedules and approaches.



Video 20 Trigeminal Neuralgia, Mid-Face

Initially, a toothpick is used to help map areas of allodynia and hyperesthesia. A 1-cm grid is created of the area. Then, 2.5 U/0.1 cc of Botox is injected intradermally at each intersecting point.



Video 21 Trigeminal Neuralgia, Lower Face

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■ S E C T I O N I V ■

Autonomic Disorders

Frey's Syndrome

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Frey's syndrome, also referred to as auriculotemporal syndrome or gustatory sweating, is a condition characterized by excessive facial sweating stimulated by the thought, sight, or consumption of food. This unusual syndrome was first described in 1923 by neurologist Lucja Frey¹ after she observed a young man whose face had been slashed with a knife subsequently develop gustatory sweating. This phenomenon frequently occurs after surgery or trauma to the parotid gland, facial nerve, submandibular gland, or thoracic sympathetic chain. It is also associated with polyneuropathies, such as those associated with diabetes mellitus, which result in inappropriate parasympathetic cholinergic innervation of cutaneous sympathetic receptors.^{2,3} The characteristic sweating results from activation of the eccrine sweat glands located in the facial area, as a result of inappropriate cholinergic stimulus from the parasympathetic

fibers of the auriculotemporal branch of the trigeminal nerve.

The incidence of Frey's syndrome after parotid surgery has been reported to be as high as 100% if tested by Minor's starch-iodine test, but only 15 to 30% of the patients consider their symptoms severe enough to report them to a physician.⁴

Numerous medical and surgical treatments have been proposed to prevent or treat this condition. Medical treatments⁴⁻¹⁵ include the application of atropine or scopolamine hydrobromide ointment before meals,⁴ and topical use of aluminum chloride in alcohol solution.¹⁶ Preventive methods at the time of initial surgery have included sternomastoid muscle flap, inclusion of the superficial musculoaponeurotic system in the flap, dermis-fat grafts, expanded polytef and temporoparietal facial flaps,¹⁷⁻²¹ surgery to raise a flap and place fascia beneath the skin to prevent further re-

innervation, and neurectomy (tympanic plexus, Jacobson's nerve, chorda tympani nerve, auriculotemporal nerve).^{4-7,22} Overall, the results have been unsatisfactory. Botulinum neurotoxin injection of the affected skin is now a first-line treatment modality for Frey's syndrome.

Intracutaneous injections of botulinum neurotoxin (Botox) have been used successfully in the management of hyperhidrosis.²³ In 1994, Drobik and Laskawj²⁴⁻²⁶ first reported the use of botulinum neurotoxin (BoNT) to treat gustatory sweating with local intracutaneous injections. In a later update,²⁷ they reported their 3-year observation of a group of 19 patients, demonstrating the mean duration of the treatment to be 17.3 months. Since that first 1994 report, more groups have reported their experience using the same method, yielding positive long-standing results. For instance, we have reported our experience with seven postparotidectomy and posttrauma patients treated with BoNT/A.²⁸ Likewise, Restivo et al²⁹ reported the effective use of the same method in 14 diabetic patients. Other, more recent reports, have shown promising results, including those from Pomprasit and Chintrakarn³⁰ assessing nine postparotidectomy patients, from Martos Diaz describing 10 patients, and from Luna-Ortiz et al³¹ reporting 23 patients who were clinically assessed for severity of symptoms based on the extent of the affected area, excessive focal sweating, and unpleasant-smelling sweat. Furthermore, Cantarella et al³² recently presented positive results from their experience with seven patients treated with

BoNT/B. In most of these cases, the patients were given a dosage of BoNT/A ranging from 1.5 to 2.5 units (U) per cc, or 80 U of BoNT/B, which yielded significant improvement of the symptoms. The majority of patients were symptom free for 6 to 12 months. After that time period, some patients experienced recurrent gustatory sweating, albeit it a decreased amount compared with that before the treatment. In those cases of recurrent Frey's syndrome, a second injection was necessary after 12 to 18 months. Most patients were permanently free of symptoms after a second or a third injection.

■ Workup

In most cases, conservative treatment has failed before patients are referred for BoNT treatment. Each patient should be counseled regarding the risks and benefits of, and alternatives to, BoNT treatment, and should sign a detailed informed consent form, which explains that BoNT injection for gustatory sweating is an "off-label" use of an approved medication.

After a careful history and physical examination, Minor's starch-iodine test is performed as follows: the patient's lateral face is painted with an iodine solution, which is then allowed to dry. Once dry, the area is dusted with starch powder. The patient is then given a sialogogue (lemon juice, grapefruit juice, etc.) to stimulate salivation. The starch turns blue-black in the area where the moisture is produced (**Fig. 17.1**).



Fig. 17.1 Starch-iodine test.

■ Anatomy

The eccrine facial sweat glands are normally activated by sympathetic fibers of the trigeminal nerve. Acetylcholine, the neurotransmitter responsible for stimulating parotid salivary production, also mediates sweat gland activation.^{33,34} Postganglionic parasympathetic fibers innervating the parotid gland (**Fig. 17.2**), as well as sympathetic fibers innervating the facial sweat glands, are severed during elevation of the parotidectomy skin flap and during the parotidectomy itself.³⁵ During the regeneration of the severed parasympathetic fibers, reestablishment of the synaptic junction occurs with the cholinergic sympathetic receptors of the sweat glands, which me-

diates sweating, flushing, and piloerection. Once the aberrant regeneration takes place, the skin will flush and sweat during eating.

■ Technique

After the starch-iodine test is performed, a grid is then created on the skin with a makeup pencil with 1-cm markings through the blue-black area (**Fig. 17.3**). BoNT/A mixed in a concentration of 1.5 to 2.5 U/0.1 mL is injected intradermally at each intersection of the grid pattern, allowing for approximately 5 to 10 mm of diffusion around each injection. The skin is then cleaned, and the patient is asked to return in 2 to 4 weeks.

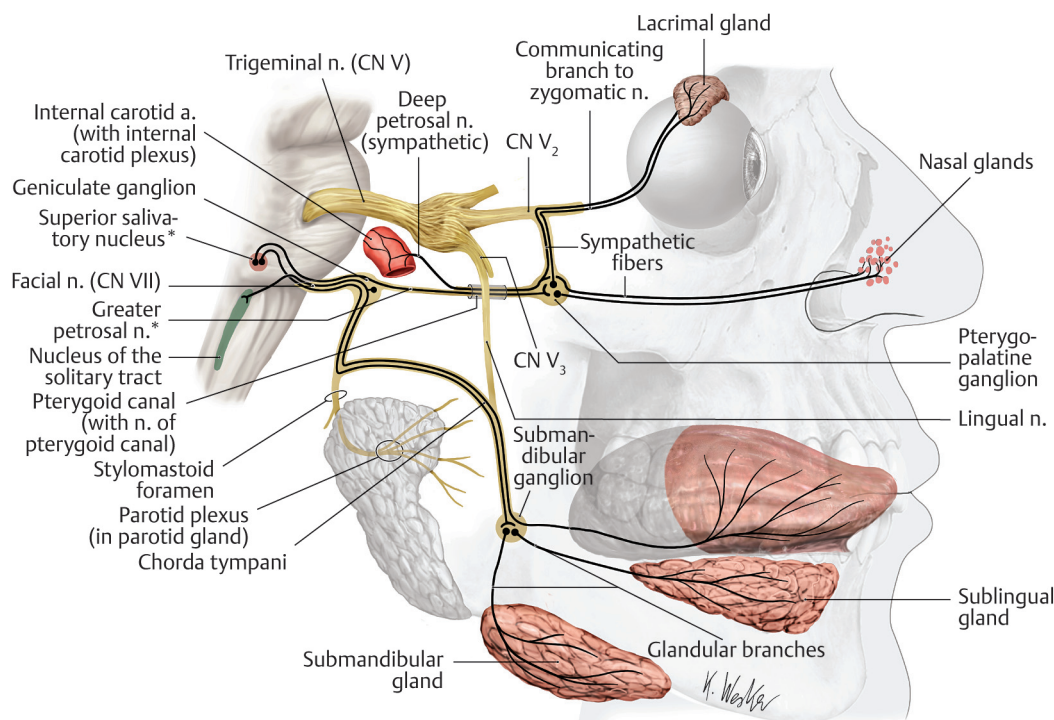


Fig. 17.2 Postganglionic parasympathetic fibers innervating the parotid gland. (From Atlas of Anatomy, © Thieme 2008, Illustration by Karl Wesker.)

■ Follow-Up

On the return visit, the starch-iodine test is repeated. Any area showing persistent gustatory sweating is reinjected using the same technique. The toxin effect begins to take place within the first 2 to 3 days, and the maximum effect occurs at 10 days to 2 weeks.

The third treatment is performed 6 to 8 months later if the patient is symptomatic. As aforementioned, most patients experience nearly complete resolution of their symptoms after two to three treatments, as opposed to other BoNT treatments that must be repeated to maintain results. Laskawi et al²⁷ sug-

gested that three mechanisms could be responsible for this observation: (1) the long duration of chemical denervation may partially or completely abolish sweat gland function; (2) these autonomic nerve fibers, once chemically denervated, are regenerated feebly or not at all, and therefore some patients will be free of symptoms subjectively, although Minor's starch test will show some positive areas; and (3) postsurgical or posttraumatic local changes in the tissue may compromise regenerating axon terminals. This could explain the variability in regeneration time and therefore the variability in intervals between treatments in different patients.



Fig. 17.3 Marking the injection grid.

■ Complications and Pitfalls

No evidence of major adverse effects has been shown in any of the reports. Mild local facial weakness may occur as evidenced in one of our patients with difficulty chewing. Dry mouth was also noted in some patients. It is interesting to note that one patient observed relief of his long-standing trigeminal neuralgia after the treatment.³⁶

Other uses of BoNT, such as for treatment of movement disorders or for cosmetic reduction of facial wrinkles, require the treatment to be repeated on average every 3 to 4 months. However, as noted by various authors, in the treatment of Frey's syndrome the time intervals between injections are much longer.

■ Conclusion

Based on our experience as well as those of other groups, we recommend the use of intradermal injections of BoNT as a safe and efficacious treatment for gustatory sweating. It is a simple office procedure that uses Minor's starch-iodine test as a guide to injection. The duration of the results is greater than 4 months and may be permanent in some patients.

The advantages of using BoNT intracutaneous injections over other methods of treatment for Frey's syndrome are numerous: the treatment requires only a simple office visit, causes minimal discomfort, achieves results within 2 to 3 days, has minimal adverse effects, and can be repeated safely whenever required even if only minimal adjustments are needed.



Video 22 Frey's Syndrome

A starch-iodine test is first performed by painting the area of the face with iodine. Once dry, starch powder is dusted over the area. The patient is then given a sour lemon candy and as the sweat accumulated, it mixes the iodine and starch producing a dark area. Once delineated, a marking pen is then used to create a 1-cm grid. At each intersection of the grid, 2.5 U/0.1 cc of Botox is injected intradermally. The patient is brought back at two weeks and another starch-iodine test is done to see if there is any residual sweating. If so, additional toxin may be injected.

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Facial Hyperhidrosis

Daniel Novakovic and Andrew Blitzer

Hyperhidrosis is a common condition characterized by perspiration in excess of that required to regulate body temperature. It may be divided into primary and secondary forms. Primary (idiopathic or essential) hyperhidrosis is a focal disorder usually involving the palms, soles of feet, axillae, or face.^{1,2} The onset of primary hyperhidrosis is usually during adolescence, and 30 to 50% of affected individuals report a positive family history, which suggests a genetic component. The genetic locus in primary palmar hyperhidrosis has been localized to chromosome 14.³ Sweating episodes may be triggered by various factors including spicy foods, emotional stressors, and mental or physical activity, but do not occur during sleep. These episodes can cause significant social and occupational dysfunction, as well as psychological stress. Secondary hyperhidrosis is characterized by generalized perspiration and is usually related to excess

adrenergic stimulation due to an underlying disease such as endocrine dysfunction, neoplasia, or chronic infection.⁴ Autonomic dysfunction associated with neurologic disorders and medication side effects are less common causes. Gustatory hyperhidrosis (Frey's syndrome) is a secondary focal variant most commonly seen after parotid gland surgery. It is discussed in Chapter 17.

Topical medical therapies for hyperhidrosis are available, but the results are often unsatisfactory. Topical aluminum salts in a concentration of 20 to 25% are an effective first-line treatment, but localized burning, stinging, and irritation may limit their use.⁵ Iontophoresis is a second-line therapy that involves delivering ions through the skin using electrical current. Local irritation and the fact that it is time-consuming limit the use of this modality.

Systemic drugs are primarily indicated in the treatment of secondary hyperhi-

drosis. Anticholinergic medications, including glycopyrrolate, oxybutynin, propantheline bromide, and benztropine, have been used with some success. Unfortunately, due to the relatively large doses that are required, a significant side-effect profile exists. Common side effects, including dry mouth, blurred vision, tachycardia, and urinary retention, limit the clinical efficacy of oral anticholinergic medication.⁶

Surgical treatments can be effective, but involve considerable risk. Endoscopic thoracic sympathectomy involves resection or ablation of the sympathetic ganglia. Reported response rates are high, with up to 86% of patients noting improvement in their quality of life.⁷ The response appears to be lower in plantar hyperhidrosis. The usefulness of surgery is limited by a high incidence of compensatory hyperhidrosis usually on the torso and lower limbs in up to 86% of patients.⁶ In addition, there is the risk of other more serious complications including Horner's syndrome and neuralgia.⁵ Other surgical therapies exist, such as removal of axillary glandular tissue, but are not appropriate in the craniofacial region.

Botulinum neurotoxin (BoNT) irreversibly blocks presynaptic acetylcholine release at the neuromuscular junction, thus exerting its muscular paralysis effects. Because acetylcholine is also the primary neurotransmitter responsible for transmission at the cholinergic neurosecretory junction, BoNT has also been shown to be a safe and highly effective method of abolishing focal sweating in idiopathic hyperhidrosis. BoNT exerts its

effects in a similar way by cleaving presynaptic SNARE proteins at two different sites. All of the A toxins cleave SNAP-25, and the B toxin cleaves VAMP. In comparison to effects on muscle, BoNT has a longer duration of action in inhibiting glandular secretion, a phenomenon that is poorly understood, but is likely due to glandular atrophy.⁸ OnabotulinumtoxinA (Botox) was initially described for palmar hyperhidrosis but is also used commonly for axillary hyperhidrosis and is the only BoNT approved by the Food and Drug Administration (FDA) for treatment of hyperhidrosis.^{9–13} However, incobotulinumtoxinA (Xeomin), abobotulinumtoxinA (Dysport), and other type A toxins currently in trials will likely show similar activity.

Böger et al¹⁴ reported on the use of BoNT for idiopathic craniofacial hyperhidrosis. In this study the diagnosis was confirmed with Minor's starch-iodine test. One half of the forehead (and the associated temple) received injections of intracutaneous onabotulinumtoxinA (Medicis Pharmaceutical, Scottsdale, AZ) in 0.1-ng aliquots using the contralateral side as a control. Some 25 to 40 injections were administered depending on the size of the region. The contralateral side was then treated 4 weeks later. Eleven of 12 patients reported complete resolution of their symptoms. All patients had some degree of forehead weakness, with two patients reporting temporary brow asymmetry (lasting up to 16 weeks). Only one patient had relapsed at 9 months.

Both onabotulinumtoxinA (BoNT/A) and onabotulinumtoxinB (BoNT/B) are

effective in the treatment of hyperhidrosis. There are some pharmacologic differences between the two subtypes. There is evidence that BoNT/B has a faster onset of action and that the autonomic nervous system is relatively more sensitive to BoNT/B compared with BoNT/A.¹³ However, Rystedt et al¹⁵ investigated the effects of BoNT/A and BoNT/B on sudomotor cholinergic function and found that BoNT/A was the most potent, achieving a mean anhidrotic area per unit of 0.69 cm² at the optimal concentration of 25 units (U)/mL. Furthermore, patients tend to report more discomfort with BoNT/B, probably due to its acidity.^{15,16} Glogau¹⁷ suggested that the diffusion characteristics of BoNT/B were better than those of BoNT/A for axillary and palmar hyperhidrosis in that it diffuses more evenly.

Despite the possible greater autonomic affinity of BoNT/B, we do not routinely employ it for facial hyperhidrosis. Its duration of action tends to be shorter than that of BoNT/A, and its greater diffusion may lead to more locoregional side effects in the head and neck, including dry mouth, mydriasis, dry eyes, and facial muscular weakness. Several studies have also suggested that BoNT/B produces more systemic side effects when compared with BoNT/A.¹⁶

■ Workup

A comprehensive history is essential to distinguish primary from secondary hyperhidrosis. The history should include the location of sweating, age at onset,

causative factors, and family history, as well as a review of systems aimed at identifying associated symptoms that may indicate a possible secondary etiology. Generalized hyperhidrosis should prompt referral for endocrine workup, which may include thyroid function tests and catecholamine levels. The diagnosis of focal idiopathic hyperhidrosis can be confirmed by a starch-iodine test, which, although not strictly necessary, allows correct mapping of the affected areas and identification of problem areas requiring further injections in the event of treatment failure.

■ Anatomy

Eccrine glands are responsible for the production of sweat—a clear, odorless, hypotonic fluid. The gland itself is a long branched structure with a coiled secretory region and a straight ductal region.^{1,2} Eccrine glands are found in highest concentration on the soles of the hands and feet, closely followed by the forehead, axillae, and cheeks. They are innervated by cholinergic fibers from the sympathetic nervous system and assist with regulation of body temperature.

■ Technique

The patient is seated comfortably in a reclining chair. The selection of treatment areas is based on patient history and physical examination identifying the most active regions. A starch-iodine test may optionally be performed to im-



Fig. 18.1 Marking a 1-cm × 1-cm injection grid of the hypersecretory region.

prove accuracy (see Chapter 17). In the active areas of hyperhidrosis a 1-cm × 1-cm grid is drawn using marker pencil or eye liner (**Fig. 18.1**). Local anesthesia is not routinely used. Injections are administered using a 1-mL tuberculin syringe attached to a 32-gauge needle. OnabotulinumtoxinA is used in a dilution of 2.5 U per 0.1 cc, as this concentration has been shown to have the most enhanced anticholinergic effect.¹⁵ Aliquots of 0.1 cc are delivered intradermally to each point on the grid where the lines intersect. Special attention must be paid to creating the characteristic intradermal “bleb” with each injection, unlike the subcutaneous “wheal” commonly created during intramuscular facial injections. Excessive pressure is to be avoided to minimize diffusion into underlying musculature.

The forehead region is typically treated first as it has the highest concentration of eccrine glands and is the most common area of excess sweat production.

■ Follow-Up

Patients are reviewed at 3 weeks to monitor progress and adverse effects. Further “touch-up” injections can be administered at this point using the same technique with the aid of a starch-iodine test. After a satisfactory response, follow-up is on an as-required basis.

■ Complications and Pitfalls

Diffusion to the underlying musculature causing associated paralysis may occur

as a side effect of treatment. In the forehead region, this phenomenon is almost universal, but is usually of little clinical significance.¹⁴ Care must be taken to avoid asymmetry of the brow or active forehead movement. In addition, injection too close to the lateral brow may cause ptosis. Thus, the forehead region lateral to the pupil and within 2 cm of the eyebrow should be avoided. The middle and lower face should be approached with increased caution, due to the possibility of adversely affecting cosmesis and function associated with underlying facial musculature. Careful intradermal injection results in improved efficacy and decreased unwanted side effects. A thorough history and physical examination are important to identify symptoms and signs of secondary hyperhidrosis.

■ Conclusion

Botulinum neurotoxin is a safe, effective, durable, and reliable treatment with minimal unwanted side effects when used for facial hyperhidrosis in symptomatic patients who have failed more conservative medical treatment and do not wish to undergo surgery.

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Sialorrhea

Scott M. Rickert and Andrew Blitzler

Sialorrhea is defined as salivation beyond the lip margin. Sialorrhea are considered normal in infants, and it typically stops in the second year of life. Sialorrhea is considered pathologic when it presents in patients who are 4 years old or older.

Sialorrhea is a common disorder found in adult patients with neurologic deficits (stroke, amyotrophic lateral sclerosis [ALS], Parkinson's disease) and in children and adults who are neurologically impaired (cerebral palsy, mental retardation, etc.). It is predominantly due to poor oral/facial muscular control in combination with hypersecretion, poor posture, and poor occlusion.

In a normal adult, approximately 1.5 L of saliva is produced daily. The six major salivary glands—the bilateral parotid, submandibular, and sublingual glands—produce 90% of the total saliva. Hundreds of minor salivary glands throughout the oral cavity and oropharynx

produce the rest. At baseline, approximately 70% of the total production comes from the submandibular and sublingual glands. When fully stimulated, the salivary production can increase five times, with the parotid gland production increasing dramatically.¹ Saliva provides important oral function by lubricating food boluses, providing amylase for initial food breakdown, and preventing local infection through its bacteriostatic and bacteriocidal properties.

The neurologic pathways for salivation arise from the parasympathetic nervous system, which originates its signals in the pons and medulla. The preganglionic fibers synapse in the otic and submandibular ganglions and then travel postganglionically to the parotid gland (via the otic ganglion) and the submandibular and sublingual (via the submandibular ganglion). Sympathetic muscular contraction enhances the expression of saliva when stimulated.

The complications associated with sialorrhea include dehydration, foul odor, and poor oral/perioral hygiene, which can lead to frequent local infections. These complications lead to many psychosocial issues such as isolation, poor social standing, and further dependency of care, and provide barriers to normal socialization (unable to share toys due to excess salivation). As these patients typically have other pressing medical issues as well, sialorrhea is frequently overlooked as a potentially treatable problem. A team approach to sialorrhea,² including providers from primary care, dentistry, neurology, otolaryngology, and occupational therapy, has been shown to result in improved outcomes.

There are several different etiologies of sialorrhea, often acting in combination: neuromuscular dysfunction, hypersecretion, sensory dysfunction, and motor dysfunction. Parkinson's disease is the most common etiology in adults. Pseudobulbar palsy, bulbar palsy, facial nerve paralysis, and stroke are less common causes. In children, cerebral palsy and mental retardation are the most common etiologies.

Hypersecretion is typically caused by teething, dental caries, or oral infections. Medications, reflux, and toxins are other possible causes of hypersecretion. Poor swallowing function is seen frequently in patients with Parkinson's disease. Anatomic abnormalities such as macroglossia and malocclusion, surgical changes, and neurologic changes such as facial paralysis all can adversely affect oral competence and management of increased secretions.

■ Workup

Evaluation of sialorrhea should include a thorough history and physical examination to characterize the severity and frequency as well as measure the degree of detriment to the patient's quality of life. Noting the characteristics of the drooling—its consistency and flow patterns throughout the daytime on a typical day—is important to help formulate an effective treatment plan.

A comprehensive head and neck examination, with specific emphasis on the neurologic component, is crucial in devising a successful treatment plan. Head position, tongue size, tonsil size, adenoid size, perioral skin condition, dental health, mandibular position, malocclusion, nasal obstruction, and the presence of mouth breathing are important anatomic factors. Neurologic signs such as tongue thrusting, hyposensitive and hypersensitive gag reflex, swallowing inefficiencies, laryngeal hyposensitivity and hypersensitivity, and tongue mobility are very important to note. Flexible nasopharyngeal laryngoscopy is an important component of the examination to fully assess the upper airway for anatomic or neurologic abnormalities.

Sialorrhea can be measured by subjective scales and objective measures (**Table 19.1**).

■ Anatomy

Sialorrhea predominantly comes from the major salivary glands—the bilateral parotid glands and the bilateral sub-

Table 19.1 Subjective Scales and Objective Measures of Sialorrhea*Subjective Scales of Sialorrhea*

1. Drooling Quotient (DQ): 40 observations in 10 hours;
DQ = percent of observations with drooling present
2. Teacher Drooling Scale
 - 1 = no drooling
 - 3 = occasional drooling
 - 5 = constant wet saliva leaking on clothing/furniture
3. Thomas-Stonell/Greenberg Assessment of Drooling²³:

Severity:

 - 1 = Dry
 - 2 = Mild (wet lips)
 - 3 = Moderate (wet lips/chin)
 - 4 = Severe (damp clothing)
 - 5 = Profuse (clothing, hands, furniture are wet)

Frequency:

 - 1 = Never drools
 - 2 = Occasionally drools
 - 3 = Frequently drools
 - 4 = Constant drools
4. Wilkie and Brody Assessment of Drooling²⁴:

Excellent: normal salivary control

Good: slight loss of saliva ± dried lips

Fair: significant residual saliva loss or perioral thickened froth

Poor: failure to control/too dry

Objective Measures of Sialorrhea

1. Radioisotope scanning²⁵: collection at chin for designated time period
2. Salivary flow rate (mL/min): use of dental rolls at orifice, and measurement of weight difference after designated time period

mandibular glands (**Fig. 19.1**). The submandibular glands lie superior to the digastric muscles in the anterior neck. There is a superficial and deep lobe associated with each gland, which is separated by the mylohyoid muscle. Typically, the deep lobe contains the majority of the gland. Secretions emanate from the gland and follow Wharton's duct on the gland's superior surface, crossing the lingual nerve and traveling anteriorly to drain just lateral to the lingual frenulum in the floor of the mouth.

The parotid glands lie between the zygomatic arch and the angle of the mandible just anterior-inferior to the exter-

nal ear. It is shaped as a pyramid directed inferiorly. Landmarks near the parotid include the styloid process medially, the posterior belly of the digastrics medially and inferiorly, the mandible anteriorly, and the sternocleidomastoid posteriorly.

Three major structures run through the parotid gland: the facial nerve and its associated branches, which separate the superior lobe from the deep lobe of the parotid; the maxillary and superficial temporal artery branches of the external carotid artery; and the retromandibular vein.

Salivary flow from minor ductal structures coalesces in Stensen's duct and

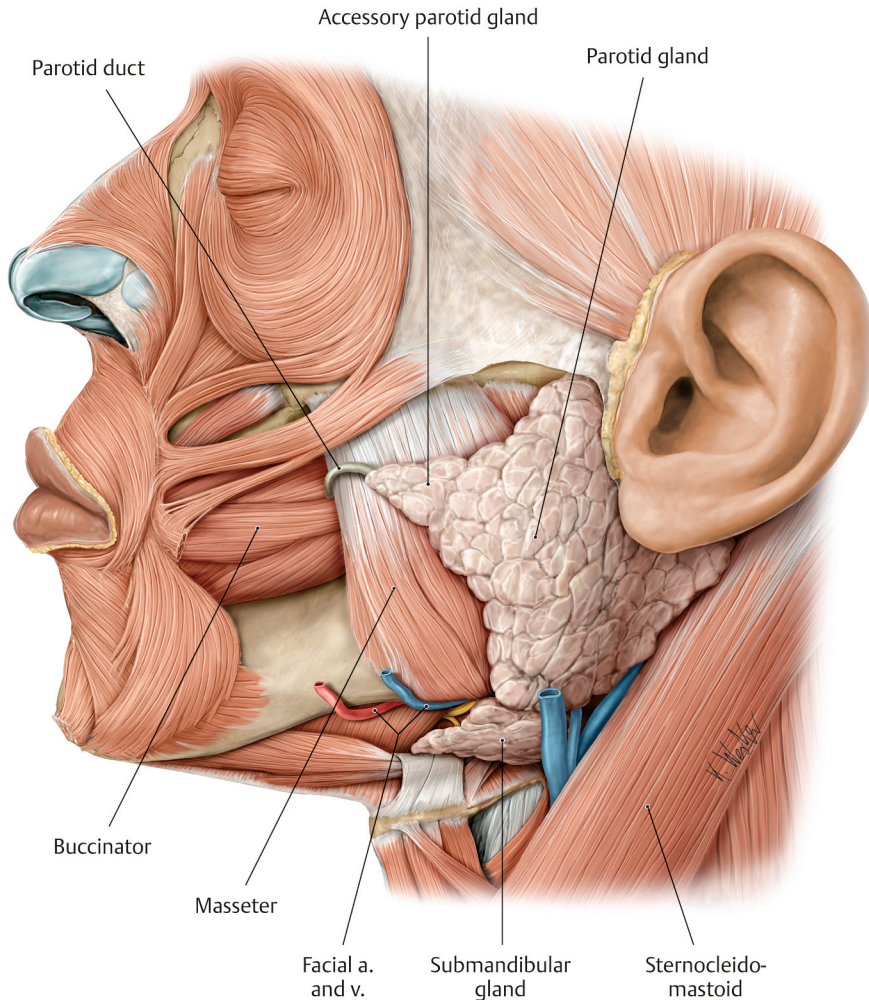


Fig. 19.1 The submandibular gland. (From Atlas of Anatomy, © Thieme 2008, Illustration by Karl Wesker.)

drains medially and anteriorly to the oral mucosal orifice just adjacent to the second upper molar bilaterally.

■ Technique

A team approach to the treatment of sialorrhea is typically the most successful.¹ Occupational therapists and speech pathologists work to improve the swal-

lowing mechanics and help to provide posture support through exercises or devices such as the head-back wheelchair. The dentist treats any malocclusion issues as well as oral decay. Orthodontic appliances or customized palate inserts can aid in better oral competence. The primary care and social work team works to improve basic quality-of-life issues that impact the patient. The otolaryngology team works to correct any

anatomic abnormalities such as adenotonsillar hypertrophy, nasal obstruction, and macroglossia that may contribute to sialorrhea. Neurologists help to identify any neuropathologies associated with sialorrhea to plan appropriate oral medications that would aid in the treatment plan.

When all of the team members have met to discuss the patient's various problems, an overall plan of treatment is devised with the patient's input. Treatment options range from conservative (observation, postural changes, biofeedback treatment) to more aggressive measures of medication, radiation, and surgical therapy.

Anticholinergic medications are effective in reducing drooling, but can be limited by side effects. BoNT/A injections into the parotid and submandibular glands are safe and effective,³ but repeat injections are necessary as the effect is temporary. Surgical intervention, including salivary gland excision, salivary duct ligation, and duct rerouting, provides the most effective, permanent treatment of significant sialorrhea to improve the patient's quality of life.⁴ Typically, the treatment begins with the least invasive option, and progresses, if necessary, to more aggressive options.

Noninvasive Techniques

Observation is an option for patients with minimal issues or with unstable neurologic function.¹ Children under the age of 4 are also typically observed if the sialorrhea is not significant. Feeding programs and exercises geared toward

better oromotor control can be initiated for those able to follow a program.

Biofeedback has been shown to be successful in patients with mild neurologic deficits related to sialorrhea and in patients over 8 years of age.⁵ The drawback is that these patients typically become habituated to the feedback, with less efficacy over time if the device feedback is not altered.⁶ Further positive and negative reinforcement can help as an adjunct method to provide sialorrhea control. These measures usually result in mild improvement.⁷

Plates can be designed to aid in better lip closure^{8,9} for those with poor closure. Beads can be placed on the upper plate and can also be used to stimulate tongue movement and redirect saliva toward the pharynx with moderate success.^{10,11}

Acupuncture of the tongue has shown a limited subjective improvement in a small study.¹² Although further study is warranted, this modality is a minimally invasive technique for those unable to tolerate more invasive methods.

If none of these noninvasive methods ameliorate the sialorrhea, then it may be necessary to proceed to more invasive techniques such as oral medications, BoNT, radiation treatment, and surgical intervention.

Anticholinergic Medication

Anticholinergic medications work by blocking the parasympathetic innervation of the salivary flow. Both glycopyrrolate and scopolamine have been shown to be effective. As always, anticholinergics are contraindicated in patients with

glaucoma, obstructive uropathy, gastrointestinal motility disorders, or myasthenia gravis, and are frequently poorly tolerated in elderly patients. Unfortunately, both glycopyrrolate and scopolamine also have side-effect profiles that are so severe that over 30% of patients are unable to tolerate these medications. For example, 23% of patients taking glycopyrrolate have significant behavioral changes,¹³ and a significant number of patients taking scopolamine or glycopyrrolate note urinary retention and blurred vision.^{13,14}

Botulinum Neurotoxin

Because of the relatively high side-effect profile for anticholinergic medications, BoNT is the primary modality in the nonsurgical treatment of sialorrhea. It not only blocks acetylcholine release at the neuromuscular synaptic end plate, but also blocks cholinergic parasympathetic secretomotor fibers of the salivary glands. Several series and one randomized controlled clinical trial assessing the ability of BoNT to ameliorate sialorrhea in patients with ALS have been published since 2000.¹⁵ Jackson et al¹⁶ performed the only randomized double-blind study using BoNT/B with electromyography (EMG)-guided injection, to avoid inadvertent intramuscular injection. They showed statistically significant improvement of both subjective and objective measures of sialorrhea at 4 weeks, and a strong trend toward benefit at 8 weeks. Additional prospective, randomized trials of BoNT for sialorrhea in a heterogeneous group of neurologic

disorders¹⁷ and Parkinson's disease¹⁸ have shown similarly positive results. Furthermore, Lim and Choi¹⁹ reported that injection of BoNT at the site of a salivary gland fistula decreased the time to full recovery.

Typical doses reported in the literature range from 5 to 50 units (U) of BoNT/A (or rough equivalent) per gland. In our practice, we have found that moderate doses injected with ultrasound guidance, and follow-up injections as necessary, have provided satisfactory results. Although BoNT can be injected solely into the parotid gland, it has been noted to be more successful at controlling sialorrhea when injected into both the submandibular and parotid glands. Injections may be performed using “blind” palpation of the gland, EMG guidance, or ultrasound guidance. Some authors feel that the use of ultrasound in injecting botulinum reduces the risks of complications.²⁰ When injecting with EMG guidance, the EMG is used to avoid intramuscular injection. In the case of the submandibular gland, audible action potentials heard after the gland has been entered likely reflect activity of the mylohyoid muscle, and indicate that the needle tip has passed beyond the substance of the gland. When injecting with ultrasound guidance, the needle itself is not visualized, but the motion of the adjacent tissue can be appreciated, and a small test “wheal” will be clearly visible at the site of the needle tip (**Fig. 19.2**).

The overall preponderance of the literature supports the use of BoNT injection as a safe and effective treatment for

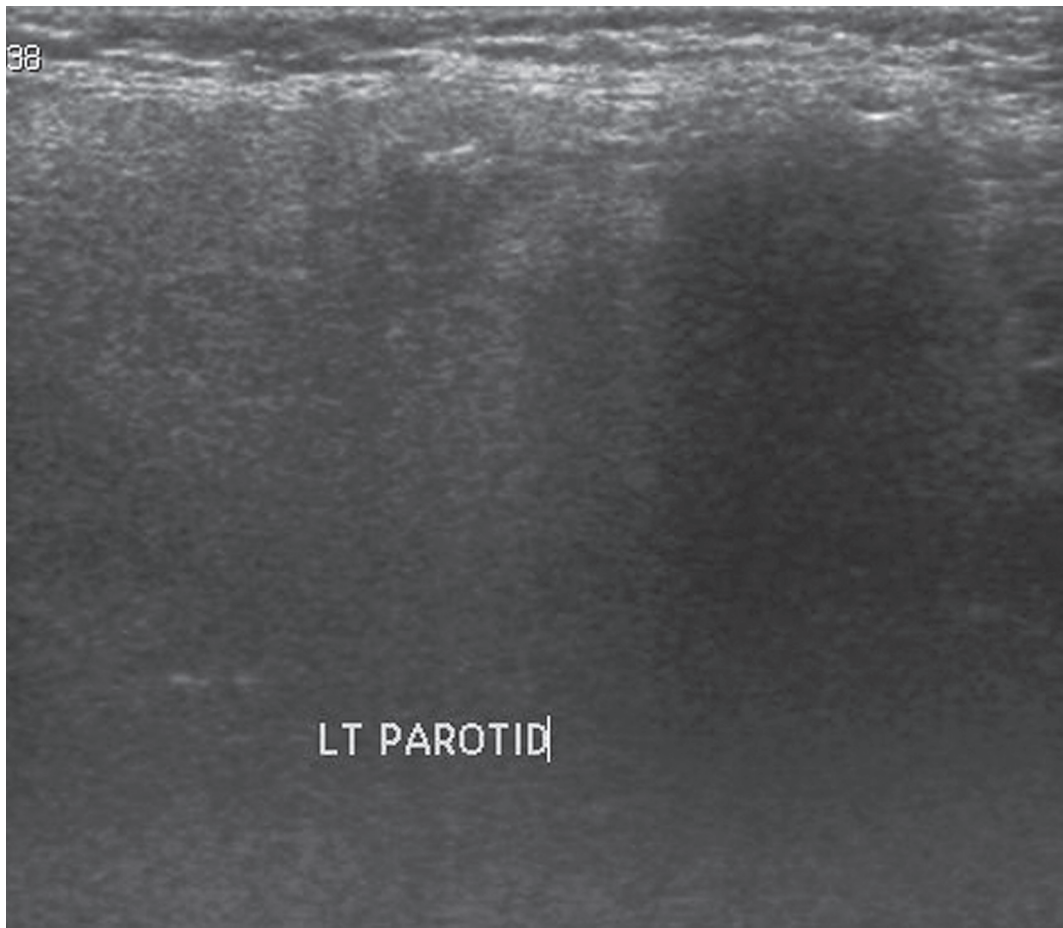


Fig. 19.2 Ultrasound-guided injection of the parotid gland.

sialorrhea. However, it is important to note that the ideal dose, the best type of BoNT, and the most effective injection method have not yet been identified. Repeated injections are necessary for long-term control, typically on the order of every 4 months (for BoNT/A).

Techniques of Botulinum Neurotoxin Injection for Sialorrhea

Once the anatomy had been identified, the patient is superficially anesthetized with either topical lidocaine cream or

injectable 1% lidocaine with epinephrine (1:100,000). The gland is palpated in one hand and the needle is directed into the substance of the gland. Careful intraoral counterpressure may be helpful, if the gland is difficult to palpate. BoNT is slowly injected throughout the substance of the gland until the desired amount of toxin is reached. If the gland is not easily palpated, ultrasonic guidance is very useful to help guide the injection. As long as the injection is within the substance of the gland, the risk of diffusion of toxin to local musculature is

low. A slow injection reduces the diffusion pressures and helps to minimize this risk.

Radiation Therapy

Aside from BoNT injections, radiation treatment to the salivary glands is another option for those patients unable to tolerate medical treatment or more aggressive surgical treatment.²¹ The dose can be titrated to the desired effect, as radiation treatment causes xerostomia. Because potential malignancies typically do not occur for 15 to 20 years after the radiation therapy, this therapy is reserved for patients who are debilitated and elderly.²¹

Surgical Treatment

There are several potential surgical treatments for sialorrhea including salivary duct rerouting, salivary duct ligation, salivary gland excision, and surgery to denervate the salivary glands. Typically, surgical intervention involves some combination of the above methods to provide a more complete and permanent solution for sialorrhea.

Submandibular or parotid duct relocation is helpful to redirect the salivary flow posteriorly to limit sialorrhea. This method can cause potential dental caries and increased risk of aspiration, but it avoids external incisions.

Tympanic neurectomy can be performed to denervate the salivary glands at the tympanic plexus in the middle ear. This is a relatively straightforward procedure and can be done with the pa-

tient under mild sedation. Due to proximity to the chorda tympani, loss of taste is a rare side effect. This intervention is usually temporary, as the nerve fibers regenerate their pathways in 12 to 18 months.²²

Excision of the submandibular glands is the most effective method to control sialorrhea and is a mainstay of surgical treatment. Typically, this procedure is performed via an external incision. Facial nerve injury, specifically the marginal mandibular nerve, is always a risk in submandibular gland excision, but the recent advent of facial nerve monitoring and the presence of good anatomic landmarks limit the risks. The most definitive surgical procedure combines the submandibular gland excision and parotid duct relocation or parotid duct ligation to limit the parotid salivary flow. It is highly successful in controlling sialorrhea, and it entails only a low incidence of facial weakness, with an improvement in the patient's quality of life.⁴ Those patients who have failed other treatment options have found good success with this most aggressive of treatments for sialorrhea.

■ Conclusion

Sialorrhea is a common problem found in both adult and pediatric populations with neurologic disorders. It is important to understand the patient's specific quality-of-life issues to better devise a treatment strategy in a team approach. Noninvasive methods, such as observation, postural changes, and biofeedback,

can aid mild cases. However, more severe cases typically require medical, radiation, or surgical treatment. BoNT injections into the salivary glands is an effective and safe short-term solution that requires repeated injections on a 3- to 4-month basis. Radiation treatment is reserved for poor surgical and medical candidates. Surgical interventions such as salivary duct rerouting, salivary duct ligation, tympanic neurectomy, and salivary gland excision are reserved for severe cases in which more conservative treatments have failed or prolonged neurologic dysfunction is expected.

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